DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE

NDA 20-919 Zeldox (ziprasidone mesylate IM, Pfizer)

Thursday, February 15, 2001

8 o'clock a.m.

Holiday Inn Gaithersburg
Two Montgomery Village Avenue
Gaithersburg, Maryland

PARTICIPANTS

Carol Tamminga, M.D., Chairperson
Sandra Titus, Ph.D., Executive Secretary

MEMBERS

Robert M. Hamer, Ph.D.
Tana A. Grady-Weliky, M.D.
Richard P. Malone, M.D.
Irene E. Ortiz, M.D.
Dan Oren, M.D.
Matthew V. Rudorfer, M.D.

VOTING CONSULTANT

Michael Grundman, M.D., M.P.H.

FDA

Russell Katz, M.D.
Thomas Laughren, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. TAMMINGA: I would like to call the meeting to order, please, the meeting of the Psychopharmacology Drug Advisory Committee. It is February 15 and we have an application from Pfizer to hear today.

In order to start out the meeting, I would like to start with introductions since our group today is a little bit different than yesterday. If you could say your name and your affiliation.

We will start with you, Dr. Oren.

DR. OREN: I am Dan Oren. I am a member of the committee and I am in the Psychiatry Department at Yale University.

DR. GRUNDMAN: I am Michael Grundman. I am a neurologist at the University of California, San Diego.

DR. HAMER: Bob Hamer, Departments of Psychiatry and Biostatistics, University of North Carolina.

DR. GRADY-WELIKY: I am Tana Grady-Weliky from the University of Rochester, Department of Psychiatry.

DR. TITUS: Sandy Titus, FDA. I am the Executive Secretary for this committee.

DR. MALONE: I am Richard Malone. I am a child psychiatrist from MCP, Hanneman University.

DR. ORTIZ: Irene Ortiz, geropsychiatrist from the

University of New Mexico in Albuquerque.

DR. RUDORFER: Matthew Rudorfer. I am a psychiatrist at the National Institute of Mental Health.

DR. LAUGHREN: Tom Laughren, Team Leader for Psychopharm at FDA.

DR. KATZ: Russ Katz, FDA, Neuropharm Drugs.

DR. TAMMINGA: I am Carol Tamminga. I am from the University of Maryland and Chair of the Advisory Committee.

Sandy Titus will now read the conflict of interest statement.

CONFLICT OF INTEREST STATEMENT

DR. TITUS: This statement is regarding Zeldox presented to us by Pfizer. The following announcement addresses the issue of conflict of interest with regards to this meeting and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research, which have been reported by the participants, present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. 208, full waivers have been granted to Drs. Tamminga, Hamer and Banister. A

copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information, Room 12A-30, of the Parklawn Building.

In addition, we would like to note that Dr. Abby Fyer has recused herself from participating in the committee's discussion and vote concerning Pfizer's Zeldox. Further, we would like to disclose that Drs. Michael Grundman, Richard Malone and Robert Hamer have involvements which do not constitute a financial interest in the particular matter within the meaning of 18 U.S.C. 208 but which may create the appearance of a conflict.

The agency has determined, notwithstanding these interests, that the interest of the government and the participation of Drs. Grundman, Malone and Hamer outweighs the appearance of a conflict. Therefore, they may participate fully in all matters concerning Zeldox.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous involvement with any firm whose products they may

wish to comment upon.

DR. TAMMINGA: Thank you.

We will start today with Dr. Laughren.

Overview of Today's Discussion

DR. LAUGHREN: Thank you, Carol. The only topic for today is the application from Pfizer for an intramuscular form of ziprasidone for agitation in patients with psychosis. This drug, of course, is well known to the committee. We discussed this last July at a meeting and, at that time, the major issue that was discussed was the finding of QTc prolongation with ziprasidone.

Also, as I am sure you are aware, we have very recently approved oral ziprasidone for marketing and, again, this is with a fairly strong warning statement about the potential for QTc prolongation.

Now, there are several issues from yesterday's discussion that I think are critical for today's discussion. In fact, if you had reached a different conclusion than you had, the discussion today may have been very brief. If, in fact, you had reached the conclusion that agitation can and should be thought about as a nonspecific symptom that needs to be studied in several different disease models, that may have been a problem for today's discussion.

But my understanding of the committee's view on this is that you think that agitation should be linked

fairly closely to the underlying disease in which it is studied rather than viewed as a nonspecific symptom like pain. Even though, obviously, many of the features of agitation with different underlying diagnoses are common, my sense was that you thought that it should, in labeling, be linked fairly closely to the underlying diagnosis.

Given that view, it seems quite reasonable to consider and discuss the ziprasidone application. Again, in fairness to the company, when we met and discussed this program with them some years ago, we, at that time, were not thinking in terms of a broader definition of agitation and the need for looking at different models so we never advised them to look at multiple models.

There are several issues that I would like you to think about as we hear today's presentation. One is the same issue that we discussed yesterday with regard to Lilly's application and that is the definition of agitation. In the ziprasidone program, as was true of the program yesterday, agitation was defined in terms of the individual investigator's judgment about what agitation was.

Patients were recruited on the basis of their being acutely agitated without, really, much further definition other than there having to have a rating of 3 or more on three out of four items from the PANSS total. Those items were anxiety, tension, hostility and excitement.

So that is really the extent of the explicit definition of agitation. So I think that is something that I will want to hear more about in terms of who was actually studied.

A related question has to do with the underlying diagnoses. As I understand it, about half of the patients in these two studies met diagnostic criteria for schizophrenia, about a third for schizoaffective disorder. The remainder were mostly bipolar although there were a few other diagnoses as well.

So one question, again, is how to characterize this population in labeling if we were to approve this application.

Finally, there is the obvious question of how to consider this application in the context of our having labeled the drug fairly strongly for this concern about QTc prolongation. It is not explicitly a second-line drug although it comes about as close as you can get to being a second-line drug.

So we will want you to discuss and consider how that should be taken into consideration in making a decision about approving this drug and labeling it.

I will stop there. Thank you.

DR. TAMMINGA: Thank you, Dr. Laughren.

We will start now with the presentation by Pfizer. Dr. Rachel Swift will start with the efficacy presentation.

Pfizer Presentation

Efficacy Issues

DR. SWIFT: Thank you and good morning, Dr. Laughren, Dr. Katz, FDA staff, Dr. Tamminga and members of the advisory committee. My name is Rachel Swift and I will be presenting the first half of the sponsor's presentation this morning.

[Slide.]

Before beginning my presentation, I would like to introduce to the committee the consultants who have helped us to understand the data collected in the ziprasidone development program and who are able to be here today to help us address your questions.

[Slide.]

What follows on the next slide is an outline of our presentation which is divided into five sections. Following and introduction and summary, I will be reviewing the general properties of ziprasidone. This will be followed by a review of the efficacy of ziprasidone.

I will then turn to Dr. Edmund Harrigan who will review the clinical safety of ziprasidone and summarize the conclusions of our presentation.

Before beginning the review of intramuscular ziprasidone, I am going to touch briefly on the medical need for treatment of agitated behavior in patients with

psychosis.

[Slide.]

As yesterday's discussions made clear, the treatment of acute agitation in psychotic patients is a common psychiatric emergency. In this setting, patients may become uncooperative and/or violent with risk of harm to themselves and others. The objectives of treatment with an intramuscular formulation are twofold. The immediate goal is rapid control of agitated behavior. The second goal is to initiate therapy for the underlying psychosis.

[Slide.]

Current therapy generally includes an antipsychotic agent or a benzodiazepine or both typically for a duration of one to three days. However, with typical antipsychotics, dystonia and akathisia commonly occur in many cases requiring treatment or prophylaxis with anticholinergic agents.

The benzodiazepines also have a number of side effects including ataxia. There is also concern about administering benzodiazepines to patients with a history of substance abuse for fear of potentiating drug dependence.

Furthermore, since the underlying psychosis requires antipsychotic treatment, polytherapy can be avoided if an effective and well-tolerated antipsychotic agent is used in this setting.

Considerations of these limitations of current therapy highlight a substantial need for improvements in the treatment of agitated behavior in this population. IM ziprasidone was developed to meet this need.

[Slide.]

Data described in your briefing document and summarized here today demonstrate that intramuscular doses of 10 milligrams and 20 milligrams of ziprasidone are effective in the treatment of agitated behavior in patients with schizophrenia and schizoaffective disorder.

The conclusion that ziprasidone IM is safe and well tolerated is supported by data collected following repeated administration at the shortest recommended time intervals at doses up to 80 milligrams daily. The safety of IM ziprasidone over three consecutive days was assessed. However, it is anticipated, based on literature and prescription data, that most patients would be treated for two days or less with the IM formulation.

Dystonia and akathisia are less frequent than with IM haloperidol. The QTc effect is similar to the oral formulation.

[Slide.]

Now I will review the general properties of intramuscular ziprasidone. Ziprasidone is a benzothiazole and a structurally unique member of the generation of so-

called atypical antipsychotic agents. The pharmacology of these drugs is complex and varied as shown on the next slide.

[Slide.]

This slide shows the relative affinities of ziprasidone, resperidone, olanzapine, clozapine and quetiapine for different receptors, each receptor highlighted in proportion to the affinity of the drug for the receptor.

This class of agents is referred to as 5-HT2-D2 antagonists and they do share this pharmacology to varying degrees of antagonism of the serotonin type 2A and dopamine type-2 receptors. However, as you can see, a comparison of the broader pharmacology of each agent within this therapeutic class reveals a wide array of differences in the relative affinities for alpha-adrenergic, histamine H1, and muscarinic receptors.

These differences predict different side-effect profiles, some aspects of which have been confirmed in the clinic. Whether these or other properties might have therapeutic implications is more speculative, but it is widely recognized that, on the basis of pharmacology alone, it is an oversimplification to lump these agents together and inaccurate to characterize ziprasidone as simply another atypical agent.

I will now describe the pharmacokinetics of IM ziprasidone.

[Slide.]

This is a high-level summary of the pharmacokinetics of IM ziprasidone which are described more fully on pages 21 to 23 of the briefing document. Effective treatment in the setting described requires a short-acting drug with a rapid onset of action.

With intramuscular administration of 10- or 20-milligram doses, ziprasidone has complete bioavailability and reaches maximal concentrations with 30 to 60 minutes post-dose. Overall exposure is dose-proportional and the half life is short. The pharmacokinetic profile allows for rapid transition to oral therapy.

[Slide.]

This slide presents ziprasidone concentrations over time following administration of single intramuscular doses of 10 and 20 milligrams in comparison to steady-state exposure observed during oral dosing with 80 milligrams twice daily. The pharmacokinetic profile following IM dosing is characterized by rapid absorption with peak ziprasidone concentrations attained approximately 30 to 60 minutes post-dose.

Based on AUC, overall exposure is dose-proportional while Cmax increases by approximately 1.6-fold

with this two-fold increase in administered dose.

Following a single 20-milligram IM dose, a mean Cmax of 249 ng/ml was attained. Dosed as recommended, mean Cmax following multiple administrations, would generally be in the range of 350 to 400 ng/ml.

The effect of elimination half life following Cmax is 2 to 4 hours. Thus, within 12 hours after dosing, ziprasidone concentrations are quite low allowing for transition to oral therapy.

[Slide.]

Figure 2 in your briefing document illustrates the clearance pathways after oral administration of ziprasidone. Ziprasidone is metabolized by two enzymes, aldehyde oxidase and cytochrome P450 3A4. Aldehyde oxidase is responsible for approximately two-thirds of ziprasidone metabolism. There are no known clinical inhibitors or inducers of aldehyde oxidase.

CYP 3A4 metabolism has been prominent in the evaluation of the drug interaction risks of other drugs including tephenadine and cisapride. In contrast to these agents, inhibition or induction of CYP 3A4 results in only a 40 percent change or less with oral ziprasidone in exposure. This is consistent with aldehyde oxidase being the predominant metabolic pathway.

Circulating metabolite exposures after

intramuscular dosing of ziprasidone are lower than those observed after oral dosing for two reasons. First, administration by the IM route avoids the first-pass hepatic extraction of ziprasidone that is responsible for the generation of metabolites following oral administration.

Second, the doses of ziprasidone recommended for administration by the IM route are lower than those administered by the oral route leading to an overall lower exposure to metabolites.

[Slide.]

I will now describe the rationale for the design of the efficacy studies and review the efficacy results. The pivotal studies are studies 126 and 125 which are both double-blind inpatient studies conducted in the U.S.

[Slide.]

It has been over two decades since a short-acting intramuscular antipsychotic formulation has been approved in the U.S. and so it is appropriate to consider the challenges unique to this area of clinical research.

The clinical challenge is to improve the treatment of agitated behavior. The research challenges are twofold. First, the appropriate patient population must be identified and, second, the effect on agitated behavior must be reliably measured.

Ziprasidone has a demonstrated antipsychotic

effect and it is preferable to initiate antipsychotic therapy as early as possible. However, an antipsychotic effect is not likely to emerge within minutes to hours of starting treatment. Furthermore, a thorough assessment of the psychotic illness would be difficult to accomplish repeatedly over the first few hours of treatment, a critical time period in the setting of acute agitation.

[Slide.]

This slide summarizes the history of the development of IM ziprasidone. There were iterative discussions and review of plans with the FDA and external experts. Consequently, the clinical-trial program was designed to focus on the agitated behavior that is often exhibited by acutely psychotic patients.

The phase III program was initiated in 1996 and the NDA filed in 1997. Based on the IM formulation being inextricably linked to the oral formulation, a not-approved letter was received in 1998.

As the committee is aware, and as Dr. Laughren mentioned, the oral formulation was reviewed in July of last year and has subsequently been approved. Discussions with the FDA regarding agitation were held last year culminating in the review today of IM ziprasidone.

I will now describe the patient population identified for entry into the pivotal IM ziprasidone

studies.

[Slide.]

All patients entering into studies 125 and 126 were diagnosed using DSM-IV as having one of the psychotic disorders listed on this slide. An antipsychotic effect had been demonstrated with the oral formulation and it was anticipated that the IM formulation would be beneficial in reducing agitated behavior in patients with psychosis.

It was intended that patients would be transitioned to oral therapy as soon as possible, hence the diagnoses of the patients entering into the IM ziprasidone studies were consistent with those of the oral protocols.

[Slide.]

To help identify a patient population appropriate for enrollment into the IM efficacy studies, the oral ziprasidone database was examined. The aim was to enroll patients into the pivotal IM studies who were acutely agitated at baseline yet well enough to provide informed consent.

The positive and negative syndrome scale agitation items of hostility, excitement, anxiety and tension were examined in the baseline scores of patients entered into two short-term fixed-dose placebo-controlled studies with oral ziprasidone.

Entry criteria for those trials specified that the

patient require hospitalization for the treatment of acute exacerbation of schizophrenia or schizoaffective disorder. Chronically hospitalized patients were excluded. This slide shows the distribution of the baseline scores in these oral ziprasidone studies for the PANSS agitation items revealing a median score of 11.

[Slide.]

This median score from the oral studies was used to establish a lower bound for the entry criteria into the IM pivotal studies. Thus, the eligibility criteria definitions were that the patient had to score greater than or equal to 3 on three of the four PANSS agitation items which insured that the lower boundary for entry into the IM pivotal studies was 10.

It should also be emphasized that all patients who were randomized into these two pivotal trials had to be judged by the responsible clinician to have a degree of agitated behavior that would be appropriately treated with IM therapy.

Patients had to be aged 18 years or older and had to be competent and able to provide informed consent to participate in the studies.

[Slide.]

This slide displays the distributions of the mean baseline scores for the PANSS agitation items for both the

oral studies, shown in blue, as well as for the two pivotal intramuscular studies shown in red. The patients enrolled into the intramuscular studies had higher median baseline PANSS agitation item scores with a corresponding shift in the distribution of scores towards higher values.

In fact, the median score of patients randomized into the pivotal IM trials was 14.

[Slide.]

Two primary efficacy assessments to capture treatment effects on behavior were utilized in the two pivotal IM ziprasidone studies. One parameter was the behavioral activity scale, or BARS. The BARS was measured at 15-minute intervals during the first hour post-injection, then at 90 minutes, two hours, then hourly until six hours post-injection.

The BARS was developed for use in the IM ziprasidone studies in 1996. It was published in the Journal of European Psychiatry in 1998 and presented at APA in May of the same year.

[Slide.]

The BARS was developed to provide an observational rating of behavior that reflects the immediate clinical status of the patient. It was designed to be quick to administer allowing frequent assessments. It is nonintrusive and does not require a patient interview.

It was anticipated that the BARS would capture the effect of IM ziprasidone on agitated behavior that was likely to be apparent within a few minutes of administration.

[Slide.]

The BARS describes seven levels of activity ranging from 1, difficult or unable to rouse to 7, violence requiring restraints. The activities in items 5 and 6 could be verbal or physical. The patient is scored based on his or her behavior at the time of examination.

The validation of the BARS is described in appendix 1 of the briefing document. The data indicate that the seven-point bars is a reliable and valid measure of activity levels in patients with psychosis and that it provides clinically meaningful information.

Excellent inter- and intra-rater reliability indicate that the BARS can be administered reliably by trained raters.

[Slide.]

The other primary efficacy measure was the clinical global impression of severity, or CGIS, a measure complementary to the BARS and more global in nature. The investigators were instructed to rate the CGIS based on the patient's behavior, specifically the severity of agitation. This was measured at four hours after the first injection

and at the study endpoint.

I will now describe study 126.

[Slide.]

Study 126 was a randomized double-blind one-day pivotal efficacy study. 79 patients were randomized to receive initial doses of either 2 milligrams or 20 milligrams IM ziprasidone with a total of up to four injections at the same dose.

Successive doses were administered at least four hours apart. The investigator could choose not to administer any further injections to the patient or to administer injections less frequently, depending upon clinical judgment.

Because the study was intended to assess acute behavioral changes rather than long-term antipsychotic effect, the duration of treatment was limited to one day. It was anticipated that the 2-milligram dose was likely to have some therapeutic effect. However, it was also anticipated that the treatment effect would be dose-related permitting a valid demonstration of efficacy.

The primary efficacy assessments were the BARS at four hours and the CGIS at four hours and last time points. The primary and secondary efficacy variables are outlined on page 33 of your briefing document.

[Slide.]

This slide summarizes the patient's baseline characteristics. The mean baseline PANSS agitation item scores were 14.3 and 14.9. The majority of the patients were men with a mean age of about 40 years made up predominantly of patients with schizophrenia or schizoaffective disorder.

[Slide.]

This graph is identical to figure 4, page 34, in your briefing document and it displays the mean BARS scores after the first injection for all patients at the observed time points. The time after first injection is given the long horizontal axis and the mean BARS scores are along the vertical axis.

The primary time point for the BARS in study 126 is four hours, the first time at which patients could receive a second dose. The blue line is the 2-milligram group. The yellow line is the 20-milligram group.

For the 20-milligram group, the mean BARS scores decreased from a baseline score of approximately 5 to 2.8 at four hours. The 2-milligram group was associated with a smaller decrease in the BARS scores to 3.8 at the same time point. The difference between the groups first reached statistical significance at 30 minutes and significance was sustained throughout the four-hour time period.

However, for the primary efficacy analysis, the

most appropriate test was not a comparison between groups at a single time point but the treatment effect observed throughout the four-hour time interval. Accordingly, it was prospectively defined in both the efficacy protocols to use the area under the curve, or AUC, of the BARS over time as a primary outcome measure.

[Slide.]

To illustrate how the BARS AUC was calculated, let's look at this graph of BARS scores over four hours as displaying the hypothetical results for one patient following his first injection. The shaded area under the line represents the AUC for that particular patient. If this patient had entered with a baseline BARS of 5 and his score had remained at 5 for every time point out to four hours, the AUC of the BARS would have been 20.

As you can see, for this hypothetical patient, since the BARS scores declined to values less than 5, the AUC of the BARS is less than 20 and is actually 12.

[Slide.]

This table summarizes the results for the primary efficacy variables for study 126 and can also be found in table 12, page 35, of your briefing document. The difference between the mean AUC BARS scores for the zero to four-hour time period in the 20-milligram group and in the 2-milligram group were significant.

The CGIS results are displayed on the next slide.

[Slide.]

This slide shows the mean change from baseline in CGI severity at hour 4 and at final assessment for both dosing groups. The mean CGI severity scores at baseline were 4.7 and 4.6 in the 2-milligram and 20-milligram groups, respectively, with a score of 4 representing moderate and 5 marked severity of illness based on the level of agitation.

The differences between the treatment groups at both the 4-hour and the final assessment time points were again significant. Hence the results of study 126 demonstrated the efficacy of 20 milligrams IM ziprasidone in all the primary efficacy measures.

[Slide.]

To provide more information on the onset-of-treatment effect, a Kaplan-Meier analysis of time-to-first-response was performed. This graph shows the proportion of patients who achieved a two-point reduction in BARS scores following their first injection in study 126 up to the 4-hour time point.

50 percent of patients achieved this prospectively defined response within one hour of receiving a 20-milligram dose. Further information regarding the onset of response can be obtained by looking at the percent of responders at each time point which is presented on the next slide.

[Slide.]

Using the same definition of response, this graph displays the percent of responders in each group at each time point. The 90-minute time point was prospectively identified as a primary comparison between groups. However, as shown on this slide, statistically significant differences in the proportion of responders favored the 20-milligram dose group as early as 45 minutes or 0.75 hours and at each subsequent time point to four hours.

I will now describe study 125.

[Slide.]

Study 125 was very similar in design to study 126. 117 patients were randomized and received an initial dose of either 2 milligrams or 20 milligrams of IM ziprasidone. Successive injections of the same dose of IM ziprasidone were administered at least two hours apart.

The investigator could choose not to administer any further injections to the patient or to administer injections less frequently depending upon clinical judgment. A maximum of four doses per patient was allowed during the 24-hour treatment period.

The study duration was one day, as in study 126. The primary efficacy assessments were the BARS at two hours and the CGI severity at four hours and last time point. The primary and secondary efficacy variables are outlined on

page 33 of your briefing document.

[Slide.]

The patient population entered into this pivotal study was similar to that entered into study 126. The mean baseline PANSS agitation-item scores were 14.9 and 15. The majority of the patients were men with a mean age of about 40 years made up predominantly of patients with schizophrenia or schizoaffective disorder.

[Slide.]

This graph mirrors the earlier one presented for study 126 and is identical to figure 5, page 36, in your briefing document. It displays the mean BARS after the first injection for all patients at the observed time points. The time post-first-injection is given along the horizontal axis, the mean BARS along the vertical axis.

The primary time point for the BARS in study 125 is two hours, the first time at which patients could receive a second dose. The blue line is the 2-milligram group. The green line is the 10-milligram group.

For the 10-milligram IM ziprasidone patients, the mean BARS scores decreased from approximately 4.8 at baseline to about 3.2 at two hours after the first injection. The 2-milligram dose was associated with a smaller decrease in the BARS scores from approximately 4.7 at baseline to 3.9 at two hours.

The difference between the groups was statistically significant at 15 minutes and then, again, at the one-hour and subsequent time points. As described for study 126, it was prospectively defined that the AUC of the BARS over time was a primary outcome measure.

[Slide.]

This table provides the results for the primary efficacy variables for study 125 and can also be found in table 14, page 37, of your briefing document.

The difference between groups in the AUC of BARS scores for the zero to two-hour time period following the first injection was highly significant. The CGIS results at the four-hour and the last time point were not significant.

[Slide.]

This slides shows the mean change from baseline in the CGIS at hour 4 and at final assessment for both dosing groups. The mean CGI severity baseline scores were 4.4 and 4.2 in the 2-milligram and 10 milligram groups respectively. In this study, second injections were permitted prior to the four-hour time point. The differences between the treatment groups were not significant at either time point.

[Slide.]

Further information on the onset-of-treatment effect is provided by looking at the time to first response. This graph presents the results of Kaplan-Meier analysis of

time-to-first-response in all patients over zero to two hours for study 125.

In this analysis, patients given the 10-milligram dose reach response criterion--i.e., a two-point decrease from baseline in BARS--in significantly less time than those given the 2-milligram dose. 50 percent of patients responded within two hours of receiving a 10-milligram dose.

This difference between treatment groups is apparent in a display of the percent of responders at each time point which is presented on the next slide.

[Slide.]

As stated earlier, a decrease of at least two points on the BARS was prospectively defined as a clinically meaningful improvement or response. As shown on this slide, statistically significant differences in the proportion of responders favored the 10-milligram dose group as early as 30 minutes or 0.5 hours and at each subsequent time point to two hours.

[Slide.]

The pivotal studies were deliberately designed to be identical except for the dose regimen so that their result could be compared. To provide further information on whether a dose-response relationship was seen in the findings across the two studies, the BARS results and the percent of responders were examined.

This slide displays the mean BARS scores after the first injection for all patients in studies 125 and 126. The time after first injection is given along the horizontal axis and the mean BARS scores along the vertical axis.

Results are given up to the primary time points in each study; i.e., two hours and four hours for study 125 and 126 respectively. The two blue lines are the 2-milligram dose groups in each study. The green line is the 10-milligram group in study 125 and the yellow line is the 20-milligram group in study 126.

The 10-milligram and 20-milligram doses result in larger decreases in the BARS scores from baseline than the 2-milligram groups of each study. The 20-milligram dose has a greater effect than the 10-milligram dose. This presence of a dose response is supported by the responder analysis displayed on the next slide.

[Slide.]

This slide displays the percent of responders at 90 minutes after the first injection by dosing group. The responders are plotted along the vertical axis and the ziprasidone dose in milligrams along the horizontal axis. The percent of responders was determined by using the prospectively defined definition of response as a decrease of two points or more in the BARS from baseline.

The time point of 90 minutes was prospectively

defined in the protocols as the time point at which to compare the responders. These results suggests a dose-response relationship for IM ziprasidone.

[Slide.]

At yesterday's meeting, we heard questions on the number of patients requiring only one injection. This slide shows the percent of patients receiving one injection only in studies 125 and 126. 24 percent and 37 percent of patients in the 2-milligram and 10-milligram groups, respectively, in study 125, were administered one injection only. 26 percent and 41 percent of the 2-milligram and 20-milligram patients, respectively, received one injection only in 126.

[Slide.]

Overall, therefore, the efficacy of ziprasidone IM has been demonstrated in two double-blind parallel group trials. Ziprasidone is effective in the treatment of agitated behavior as evidenced by a reduction in BARS scores. These results demonstrate an onset as early as 30 minutes as well as a dose-related effect.

The effectiveness of the 20-milligram dose on agitated behavior was also demonstrated by improvement in the CGIS results. The data derived from studies 125 and 126, taken together, provide robust evidence of the ability of IM ziprasidone to calm, in a dose-related manner,

agitated psychotic patients.

I will now review the findings from study 306.

[Slide.]

Study 306 was designed to provide information on how IM ziprasidone would be used in clinical practice and to compare the properties of ziprasidone with haloperidol. The feasibility of conducting a double-blind flexible dose comparative study was explored. However, investigators were not comfortable with randomizing acutely ill patients to treatment with 2.5 milligrams of haloperidol, a dose with the equivalent volume of 10 milligrams ziprasidone.

Thus, the flexible dose design led to the 306 study being open label. Patients required hospitalization for acute psychosis and received IM dosing for up to three days depending on clinical need followed by four days of oral therapy.

90 patients were randomized to receive ziprasidone and 42 to receive haloperidol. A number of safety and efficacy assessments were performed. Efficacy assessments included the brief psychiatric rating scale, BPRS, and the CGIS. The BARS was not used in this study which was conducted outside of the U.S.

I will now describe the patients entered into study 306.

[Slide.]

The demographics of the patient population entered into study 306 were similar to those entering into the other IM ziprasidone studies. The majority of the patients were men with mean ages in the early to mid-thirties. The mean baseline BPRS scores were 45.9 and 47.5 in the ziprasidone and haloperidol groups, respectively.

[Slide.]

This table shows the mean doses in milligrams per day and the number of injections per day in the two treatment groups. In this trial, the most frequently administered dose of IM ziprasidone 10 milligrams. Only 18, or 20 percent, of the 90 patients required even one 20-milligram dose of ziprasidone.

The dose administered was effective, as can be seen on the next slide.

[Slide.]

This slide displays the mean changes from baseline in the BPRS totals for the two treatment groups for day 1, last IM and last oral time points. As mentioned earlier, the mean baseline BPRS totals were 46 and 47. Acknowledging the limitations of an open-label design, this data shows that the mean change in BPRS in patients treated with IM ziprasidone was significantly greater than those treated with IM haloperidol.

A full summary of the efficacy outcomes in study

306 is provided in table 16, page 42, of your briefing document.

[Slide.]

Overall, the efficacy results from studies 125 and 126 as well as the data from 306 support the wording in the Indications section of the proposed labeling which is presented on this slide. The data support the use of ziprasidone intramuscular for the acute control of agitated behavior in patients with schizophrenia and schizoaffective disorder.

[Slide.]

I would now like to introduce Dr. Edmund Harrigan who will review the data on the safety and tolerability of IM ziprasidone.

Safety Data

DR. HARRIGAN: Thank you, Dr. Swift. Good morning to members of the committee.

[Slide.]

The discussion of safety data will follow the order shown on this slide, considering first the discontinuations from clinical trials, then the adverse events and, finally, reviewing the electrocardiographic data.

[Slide.]

First an overview of the database. Nine clinical

trials were included in the NDA for IM ziprasidone enrolling a total of 671 patients. 523 of these were treated with ziprasidone, 142 haloperidol and 6 placebo. There were two phase-II studies. Study 046 was a multiple dose clinical pharmacology trial which was conducted in otherwise healthy patients with schizophrenia.

Study 120 was a phase-II open dose-ranging trial. There were four phase III studies. Three were conducted in the U.S. including the two pivotal double-blind trials which are considered pivotal for efficacy, the 125 and 126 and one open-label comparative safety trial, study 121. An additional open-label study, 306, which was just described, was performed outside the U.S. and provides support safety and efficacy data.

Additionally, study 97001, which was not completed in time for database cutoff, contributes baseline and post-baseline data to the ECG tables which you have in your briefing document.

[Slide.]

This slide shows the overall picture for discontinuations from pivotal studies 125 and 126. The completion rates range from approximately 92 to 97 percent and four patients, overall, were discontinued because of adverse events.

[Slide.]

Here you see a listing of these four individual cases. One clarification regarding the days-on-treatment column. As you have heard, these were 24-hour studies. However, some patients, many patients, participated in the trial during parts of two consecutive calendar days and so are recorded that way in the database.

Three of these events were reported as severe. The first patient who had a past history of hypertension experienced an increase in blood pressure after receiving a single dose of 2 milligrams. This elevation occurred approximately seven hours after being treated with 2 milligrams of ziprasidone.

The second patient had a past history of priapism and experienced another recurrence one week after discontinuing ziprasidone. The last patient was discontinued from study 125 because of moderate disruptive behavior and severe agitation.

[Slide.]

This slide is table 21 on page 46 in your briefing document and displays adverse events occurring with a frequency of at least 5 percent in any treatment group. Somnolence, headache, nausea and dizziness and the most frequent adverse events in ziprasidone-treated patients and appear related to dose.

All of the adverse events represented on this

table were mild or moderate in severity.

[Slide.]

Studies 125 and 126 were twenty-four hours in duration and many patients were treated with less than the maximum permitted number of four injections. However, it was recognized that at least some patients may receive IM treatment for more than one day. Therefore, the safety and tolerability of ziprasidone IM has been studied at doses up to and beyond the limit of the maximum recommended dose.

[Slide.]

This slide summarizes ziprasidone exposure within the phase-II\III IM trials. Fewer than 20 percent of patients in the IM database received less than 10 milligrams per day of ziprasidone. Just over 30 percent of patients received at least the maximum recommended daily dose of 40 milligrams and most of those for three consecutive days.

In the briefing document you have been provided safety information from the pooled studies 125 and 126 and individually for studies 306 and 121. Because study 121 examined the safety of the highest doses per day, given for the longest duration, the remainder of this presentation will focus on the findings of that study.

[Slide.]

Study 121 was a seven-day parallel group clinical trial in which patients were randomized to receive one of

three fixed doses of ziprasidone IM administered as 5 milligrams every two hours, 10 milligrams every two hours or 20 milligrams every four hours, or a flexible-dose haloperidol IM.

In the high-dose group, an initial dose of 10 milligrams was administered on the first day of treatment. Patients received intramuscular treatment for three days followed by oral dosing with the same drug for a further four days. 69, 71 and 66 ziprasidone patients were randomized to doses of 20, 40 or 80 milligrams per day, respectively and 100 patients received flexible-dose haloperidol.

The majority of haloperidol-treated patients received two injections per day and the mean total daily dose of haloperidol was 11 milligrams.

[Slide.]

This slide provides an overview of the patient population enrolled into study 121. The majority of the patients were male with a mean age of approximately 40 years with a diagnosis of schizophrenia or schizoaffective disorder in approximately 80 to 90 percent. This study was designed to enroll clinically stable patient volunteers who would be compliant with receiving three days of intramuscular dosing.

Mean baseline BPRS scores ranged from

approximately 36 to 38. In contrast, you may recall that in study 306, the mean BPRS scores at baseline ranged from 46 to 48.

[Slide.]

This slide shows the overall picture for discontinuations from study 121 during the IM dosing period. There were relatively few discontinuations and over 85 percent of patients in each treatment group completed the intramuscular treatment period.

[Slide.]

This table provides further information on patients who were discontinued for adverse events during the IM dosing period of study 121. There was no event responsible for more than one discontinuation and all of these events resolved. The only severe adverse event on this list leading to discontinuation was migraine in a patient with a prior history of migraine who was treated and responded to subcutaneous sumatriptan.

[Slide.]

This slide contains the same information as supplied in table 22 in the briefing document but the threshold occurrence is cut for this slide at 10 percent instead of 5 percent as in your briefing document. The most common adverse events occurring with ziprasidone treatment were nausea, dizziness, headache and insomnia. The most

common adverse events occurring with haloperidol treatment were akathisia, dystonia, extrapyramidal symptoms and hypertonia.

The vast majority of treatment-emergent adverse events reported in the ziprasidone and the haloperidol groups were mild or moderate in severity. Again, this was in study 121 with four doses per day for three consecutive days.

[Slide.]

In addition to collection of reported adverse events, the Simpson-Angus and Barnes Akathisia Scales were used to examine the potential for ziprasidone to cause or exacerbate extrapyramidal symptoms. Focussing still on study 121, in which patients were administered up to 80 milligrams daily for three days, scores on these rating scales suggest a clear distinction between ziprasidone and haloperidol which was administered, again, at a mean dose of 11 milligrams per day.

[Slide.]

There was some discussion yesterday concerning the effect of an IM treatment on blood pressure and heart rate. In study 121, blood-pressure measurements were taken in sitting and standing positions just before the administration of each dose and again at 30 and 60 minutes after each dose.

Over 10,000 measure of blood pressure were taken in ziprasidone-treated patients in that study. This slide displays the mean postural change--that is, the change which occurred after maintaining a standing position for two minutes--for each treatment group on the first day of treatment.

As you can see, at baseline, there was a small mean decrease in systolic and a smaller increase in diastolic pressure again at baseline on changing from the sitting to the standing position. There is no evidence with ziprasidone dosing that ziprasidone had a meaningful effect on postural blood-pressure change.

[Slide.]

Similarly, heart rate increases somewhat on standing in patients at baseline. You see increases of five to seven beats in the four treatment groups at baseline. This increase is enhanced by two to five beats per minute in the ziprasidone groups. The haloperidol group shows no postural change in heart rate.

The magnitude of the increase is similar to that which was measured for ziprasidone in study 054 after two weeks of oral dosing and is less than was measured with the other atypical agents in that study, particularly olanzapine with six beats per minute, risperidone nine, and quetiapine, eleven beats per minute. That is consistent with the

pharmacology that Dr. Swift showed earlier with the pie charts.

[Slide.]

Finally, we will consider the effect of ziprasidone on the ECG.

[Slide.]

The oral formulation, as has been mentioned, has been approved based on clinical and electrocardiographic data which we reviewed here in July. Just to recap and to update that data, the QTc effect of ziprasidone has been closely examined. The effect is well characterized and appears to be limited as a function of its pharmacology and the stability of its metabolism.

In the now 2005 patients years of exposure to ziprasidone, there have been no cases of torsade and no evidence of increased risk of arrhythmia-related clinical events.

[Slide.]

Some of the confidence that the effect of ziprasidone is well understood derives from an examination of the concentration effect relationship between ziprasidone and QTc. This figure is included in the ziprasidone IM briefing document. It was in the ziprasidone oral briefing document. It presents changing QTc on the vertical axis and ziprasidone concentration on the horizontal axis for 2435

data points each representing a QTc measure which was taken within one hour of a ziprasidone level.

These data, again, are from the oral ziprasidone program. The concentration axis is truncated at 400 ng/ml. In this dataset, there were nine patients who had a ziprasidone concentration above 400 ng/ml. The QTc values for these nine patients are annotated on the vertical axis so that the individual with 955 ng/ml had a QTc change of 2 milliseconds.

The patients represented on this slide were treated with a fairly wide dose range of oral ziprasidone. You recall from the comparative ECG trial, study 054, that patients treated with the highest recommended dose of ziprasidone of 160 milligrams, or 80 milligrams twice daily, experienced a mean QTc change at Cmax of approximately 16 milliseconds.

In the next slide, we return to our population pharmacokinetic database from oral phase II\III trials to examine the range of concentrations measured at Cmax in patients receiving daily doses at the top of the dose range.

[Slide.]

In the oral databases, 595 measurements at expected Tmax are available from patients who were being treated at the upper end of the oral dose range. In the intramuscular database, over 1000 serum measurements of

ziprasidone have been obtained during the first two hours following the administration of an intramuscular dose.

As indicated on this slide, 644 of those followed doses of 10 milligrams or 20 milligrams. These are displayed on the next slide.

[Slide.]

This slide displays the concentrations measured near Tmax in patients receiving the highest oral doses of ziprasidone. Below this are shown similar distribution plots of ziprasidone concentration measured during the first two hours following an intramuscular dose of 20 milligrams or 10 milligrams. The dense dots, the dense pink dots, mark the median. The box encloses 50 percent of the data and the brackets bound approximately 99 percent of the data points.

As you can see, the concentrations observed near Tmax with the intramuscular formulation are in the same range as those observed near Tmax with the oral formulation.

[Slide.]

As Dr. Swift noted very early in this presentation, the Cmax occurs more quickly following intramuscular administration than following oral administration. It is reasonable to ask whether the rate of rise or ziprasidone concentration significantly alters the concentration effect relationship between ziprasidone and QTc.

On this slide are plotted the QTc changes measured during the first six hours following 113 intramuscular doses of ziprasidone, 5, 10 and 20 milligrams, and fourteen intramuscular doses of haloperidol.

Visual inspection, particularly of QTc changes during these first two hours, reveals a fairly broad scatter of increases and decreases. Looking for a trend across time, values were grouped in two-hour intervals and averages determined as shown on this slide.

[Slide.]

This table displays mean QTc change from baseline with 95 percent confidence intervals for tracings grouped into bins of zero to two hours, two to four hours, and four to six hours.

For ziprasidone IM 5, 10 and 2-milligram doses, a mean change of 0.4, 0.9 and 6.4 milliseconds were measured compared to a mean change of 5 milliseconds following haloperidol during the first two hours of dosing. Consideration of the 95 percent confidence intervals suggest that the effect of ziprasidone on the ECG following IM administration is similar to the effect of ziprasidone on the ECG during oral administration as measured in study 054.

[Slide.]

This table, which is included in your briefing document, confirms that there were no QTc measurements of

500 milliseconds or greater and no excess of QTc measurements crossing change thresholds in the ziprasidone group compared to the haloperidol group.

[Slide.]

Overall, therefore, ziprasidone concentrations observed in the intramuscular program lie within the range observed following oral dosing. The effect of ziprasidone on the ECG following intramuscular administration appears similar to the effect measured during oral administration.

[Slide.]

To conclude, ziprasidone IM is an effective treatment for agitated behavior in patients with schizophrenia and schizoaffective disorder at doses of 10 milligrams and 20 milligrams. The safety and tolerability of ziprasidone IM have been examined over three consecutive days at doses in excess of the maximum recommended.

Ziprasidone appears to offer tolerability advantages over haloperidol IM and represents a potentially important treatment option for these patients.

Thank you.

DR. TAMMINGA: Thank you very much, Doctor Swift and Dr. Harrigan for the presentation.

Committee Discussion

The discussion of this drug is open to the committee. I would suggest that we first begin with any

questions that we have either for the efficacy database or the safety database from Dr. Swift and Dr. Harrigan.

I will start with an initial question for Dr. Swift. In the 125 and 126 pivotal studies, although you had 70 percent men, you did have 30 percent women. Did you analyze for any gender differences?

DR. SWIFT: Yes; we did. I can show you those results. We looked at those and they didn't reveal a difference between the all patients and the female patients. Can I have slide 352, please?

[Slide.]

This shows the AUC of the BARS scores for patients entered into study 125 with the all patients on the left. I'm sorry; this is the wrong slide. This is race--to answer your next question.

Slide 354, please.

[Slide.]

This slide shows all patients on the left, male patients in the middle and female patients on the right for the 2-milligram and ten-milligram groups respectively for the AUC of the BARS.

DR. TAMMINGA: When you analyze the 2-milligram dose overall, did you analyze that statistically to see if there was any significant change from baseline for just the 2-milligram dose?

DR. SWIFT: Yes; we did, and there is a treatment difference.

DR. TAMMINGA: Dr. Katz?

DR. KATZ: You showed a slide which displayed the distribution of ziprasidone serum concentrations, oral versus IM. And you showed that the mean for the 20-milligram was about 200. Was that single-dose data?

DR. SWIFT: Yes; it was.

DR. LAUGHREN: I think you had said earlier that, with repeat IM dosing, the Cmaxes are in the range of 350 to 400.

DR. SWIFT: Yes.

DR. KATZ: Was that with the 20-milligram repeat dose?

DR. SWIFT: Yes; it was.

DR. KATZ: So that is the maximum repeat dose and that is the Cmax.

DR. SWIFT: Yes.

DR. KATZ: What is the extent of experience with looking at QT at plasma concentrations around 400, either with the oral or--the graph you showed of the oral, the one that we had seen before, has very few data points after 400. I think, in fact, you said it was truncated at 400.

So I am wondering what is the experience at those plasma levels with regard to QT?

DR. HARRIGAN: Matching concentration to QTc in the IM database was--we don't have the depth of data. It was more difficult with the IM than with oral. The rapid rise and fall of the concentration makes matching ECG to a concentration more challenging. One hour was a sufficient range to match an oral concentration with an ECG.

With the IM, with the rapid rise and fall, one hour didn't seem appropriate. What we can tell you is that, for the slide that you did see in the main presentation, most of those patients, 15 out of those 17 patients who had received 20 milligrams who were shown on that slide, it was their fourth dose of 20 milligrams.

So we don't have concentrations to match those ECG datapoints, but of the ECGs we showed you in those first six hours following dosing, most of those were not after the first dose or the second dose. The slight majority were after the fourth dose.

DR. KATZ: How many patients was that?

DR. HARRIGAN: There were 27 datapoints, ECG datapoints during the first six hours following intramuscular administration of a 20-milligram dose.

DR. KATZ: Right. How many patients was that? It was 27 patients?

DR. HARRIGAN: 27.

DR. KATZ: Again, I recognize that you don't have

a lot of data, QT data, at plasma levels at around 400 with the IM experience. But I am asking how much do you have with the oral?

DR. HARRIGAN: We could put that slide back up from the main presentation.

[Slide.]

Here is the concentration axis here. It goes from 0 to 400 ng/ml. You recall that 380 ng/ml, I think, was the highest concentration experience in study 054. There are nine individuals out here who had an ECG within one hour of a ziprasidone serum concentration which exceeded 400 ng/ml, the highest being 955 ng/ml. Those are those QTc values.

DR. KATZ: Right, and the point I am trying to bring out is that, with 20 milligrams repeat dose, you get into plasma concentrations as far as Cmax at which we don't really have very much experience--can't take much comfort from the oral database because there are very few patients who have reached those concentrations.

DR. HARRIGAN: I think with the oral database what you are able to derive is a concentration effect relationship which really has to be projected out and is consistent with the admittedly more sparse data points in excess of 400 ng/ml.

DR. KATZ: Sparse is one word for it. It is extremely sparse would be another view. There were nine

patients, I think you said. Whether or not one can extrapolate beyond basically the data is the question.

DR. TAMMINGA: In this oral database, is there an increase in QT interval with dose--with plasma level; excuse me?

DR. HARRIGAN: In the oral database? If you recall, in the oral database and the short-term fixed-dose studies, there were QTc changes of 4, 6 and approximately 10 milliseconds at 40, 60 and 80 BID, so up to 160 mg/day. Then there was dose group of 200 mg/day with a mean change of about 6 milliseconds. That was the highest dose examined in the oral.

DR. GRADY-WELIKY: I was just curious if you guys had the distribution of the baseline BARS in the patients.

DR. SWIFT: We do. Actually, they are in table 1R and 3R of the FDA briefing document that was handed out. It tells you the percent of patients with baseline BARS scores for both studies 126 and 125.

DR. GRADY-WELIKY: This could be in that as well, but did you notice any difference in terms of response based on initial BARS?

DR. SWIFT: We showed a treatment effect in all patients who were entered into the 125 and 126 study. We have done an analysis where we split out the patients who had a baseline BARS of 5 or greater, which I can show you.

If you could put up slide No. 34, please.

[Slide.]

This is for study 126, all patients on the left and those patients entered with a baseline BARS score of 5 or greater on the right. The 2-milligram group is the blue. The yellow is the 20-milligram group. As you can see, significance is still seen in those patients with the higher baseline BARS scores.

I will just show you the corresponding slide for study 125 which is slide No. 33, please.

[Slide.]

As you can see, again, splitting out the subset more severely agitated patients did not affect the significance of the findings.

DR. RUDORFER: I notice that you conclude that the drug is efficacious in schizophrenia and schizoaffective disorder patients. What happened to the bipolar disorder patients?.

DR. SWIFT: If we could put up slide No. A142.

[Slide.]

As Dr. Laughren mentioned in his opening comments, 80 percent of patients enrolled had a diagnosis of schizophrenia or schizoaffective disorder. A further 10 percent had bipolar disorder. This slide shows the AUC of the BARS by primary diagnosis for the zero to four-hour

time points in study 126.

The bipolar patients can be seen here in both the treatment groups.

The corresponding slide for 125, A141, please.

[Slide.]

This shows a similar pattern.

DR. RUDORFER: So the number is too small, then, are you saying, to reach a conclusion?

DR. SWIFT: The studies were open, as you saw in the main presentation, to a variety of DSM-IV diagnoses with psychotic disorders. Since we had only enrolled 10 percent of patients with bipolar disorder, where recommending treatment was limited to the indication for patients with schizophrenia or schizoaffective disorder.

DR. KATZ: Just to follow up on that, if I read it correctly, in both of the studies there was a nominal significance between the 10 or 20 and the 2-milligram, even for the bipolar, even though the numbers are very small?

DR. SWIFT: Yes; That's correct. I was just trying not to read too much into it because the numbers are so small.

DR. TAMMINGA: Would you say a little more, Dr. Swift, about how you actually recruited patients to the study. Did you recruit specifically schizophrenics and schizoaffectives or, under the umbrella of psychosis, did

you take all comers?

DR. SWIFT: It was under the umbrella of psychosis and taking all comers. I will just put up the slide from the main presentation, No. 17.

[Slide.]

This gives you the DSM-IV diagnoses from those patients entered.

DR. TAMMINGA: In order to get this variety of people, though, the way the protocol was written, it was written for agitation in psychotic disorders.

DR. SWIFT: Yes; That's correct.

DR. TAMMINGA: These are the diagnoses that came to you. You didn't specifically go out looking for these diagnoses?

DR. SWIFT: These are the diagnoses that were listed in the wording of the protocol saying that after a patient had been judged by the investigator to be in need of IM treatment, they had to have a DSM-IV diagnosis that met one of these psychotic disorders listed on this slide.

DR. ORTIZ: Along this same line, in what kind of setting was the study conducted? Emergency rooms? Inpatient units? Psychiatric emergency room?

DR. SWIFT: Both of the pivotal studies 125 and 126 were conducted in an inpatient setting. However, a number of the patients were referred from the emergency

room. I don't have the breakdown of those numbers. So it could be somebody who was referred through the emergency room. It could be somebody who was admitted directly into the inpatient psychiatry ward, depending on the emergency-room facilities at the hospital. Or, occasionally, it was a patient who was already an inpatient who became acutely agitated.

DR. HAMER: Could we look at the baseline BARS scores again for 125 and 126, if you have that combined? If you don't have it combined, either one or both of them.

DR. SWIFT: If you give me just as moment, we will find the appropriate slide. Do we have it combined? I don't think we have the--we can certainly get that for you.

DR. HAMER: How about either one?

DR. SWIFT: No; I'm sorry. We didn't do the BARS distribution at baseline. It is in your briefing document.

DR. HAMER: It is my impression that the three extremely agitated points on the agitated end of the BARS scale, you had very few patients at that end at baseline.

DR. SWIFT: We had 90 percent of patients in study 126 and roughly 70 percent of patients in study 125 who had a BARS of 5 or greater. I will just put up slide No. 23 from the main presentation.

[Slide.]

So the score of 5 was levels of overt activity.

We didn't exclude the patients with scores of 6 or 7 from entering, however. But it is believed that this level of BARS score probably reflects an inability of the patient to provide informed consent.

DR. HAMER: The words, "signs of overt activity can be calmed," strikes me as not all that agitated. I am wondering about the extrapolation to more agitated patients.

DR. SWIFT: As you recall from the main presentation, all of the patients entered into studies 125 and 126 had to be judged by the investigator to be in need of IM treatment. They also had to meet, at screening and at baseline, minimum entry criterion on the PANSS agitation items. Also, as you saw earlier, looking at the distribution of the PANSS agitation item scores, those patients entering into the IM ziprasidone studies were more agitated than those patients entering into oral studies for acutely ill patients.

We did also do a subset, though, of patients who had higher PANSS agitation item scores at baseline which I can show you. What we did is we selected patients who scored at least 4 on three of the four PANSS agitation items.

If we could put up slide No. A36, please.

[Slide.]

This shows the AUC of the BARS over zero to four

hours for study 126 for all patients on the left and those patients with the higher PANSS agitation item scores at baseline. As you can see, the significance is maintained in that more agitated patient population subset.

If you could put up slide 35, please.

[Slide.]

This is a corresponding display for study 126 and also demonstrates that, in the more agitated patients, significance is still maintained in that subset of patients.

DR. OREN: In addition to the medication, were there any incentives offered for patients to participate in the study either in terms of offering them something or not giving them something if they would agree to participate?

DR. SWIFT: If you are referring to financial incentives for 125 and 126, no. There were no financial incentives for the patient to participate. However, they did have the opportunity, in both of the studies, to enroll in an open-label extension and to continue receiving ziprasidone orally. Half of the patients in study 125 and two-thirds of the patients in study 126 opted to enter this open-label extension study.

DR. TAMMINGA: They didn't know at that time, however, whether it was a good deal or not to stay in the study. Can you show us, Dr. Harrigan, a little bit more detail on the motor side-effect data comparing Haldol and

ziprasidone, particularly on dystonia items, even number of dystonic events?

DR. HARRIGAN: Let's look at B57.

[Slide.]

This is the incidence of adverse events during intramuscular treatment. This is, again, looking, now, at the worst case for ziprasidone, or 80 milligrams per day administered, 20 milligrams four times a day, for three consecutive days. As you have read in the briefing document, the recommended dose is 10 to 20 milligrams up to four times a day.

Looking even at that highest dose of ziprasidone, the contrast can be seen down here in terms of movement disorders, particularly addressing your question, with dystonia, extrapyramidal symptoms, hypertonia and akathisia more commonly experienced in the haloperidol group than in the ziprasidone group.

DR. TAMMINGA: What will be your recommended dose?

DR. HARRIGAN: 10 to 20 milligrams, 10 milligrams administered at least--well, every two hours or 20 milligrams four hours apart--up to 40 milligrams per day.

DR. TAMMINGA: Do you have the same data, then, for the 10 to 2-milligram dose range?

DR. HARRIGAN: We have adverse events in 306. Slide B83.

[Slide.]

Looking first at the rating scales--this is study 306, so this is a study in which patients were agitated on enrollment into the study, underwent or experienced up to three days of treatment with intramuscular medication with either drug and then transitioned to oral.

So, for the Simpson-Angus scale, you see a slight decrease from baseline in the ziprasidone group and a notable increase in the haloperidol group. The same pattern of findings for the Barnes Akathisia.

If we could look at slide B74.

[Slide.]

This is a little bit more complex slide. What we are showing you here are the adverse events during the intramuscular treatment period, in the column on the left for ziprasidone, compared to the column on the left, here, for haloperidol. Then we continued to collect adverse-event data, of course, in the oral treatment period which completed the seven-day treatment period of the protocol.

Again, particularly to your questions, during intramuscular treatment, there was a 7 percent incidence of dystonia in haloperidol, 1 percent for ziprasidone. Two patients of 90 experienced some akathisia with ziprasidone. There was 7 percent, or three patients, with hypertonia, tremor and then extrapyramidal symptoms most commonly coded

as rigidity or Parkinsonism in the haloperidol IM treatment group.

The contrast persists in the oral treatment period as well between ziprasidone and haloperidol.

DR. GRUNDMAN: Were there any differences in the tolerability based on age?

DR. HARRIGAN: Let's look at slide B62.

[Slide.]

The number of patients over age 65 was very small. We cut this database as the FDA reviewer did at age 55, or as was done in our integrated summary for safety. So here is a listing of the adverse events, the incidence greater than 5 percent in all patients treated with IM ziprasidone in the patient cohort, overall, and in patients less than age 55 and in the 45 patients over age 55.

Somewhat less headache and somnolence, slightly higher incidence of dizziness. No other real notable differences.

DR. TAMMINGA: Dr. Malone?

DR. MALONE: I can't recall, were there any concurrent medications, or what medications were the patients taking right before entry including--do you know if they were on anti-EPS medicines and if they continued on them?

DR. HARRIGAN: Let's look at B92. Yes; they were.

Actually, let's look at B91.

[Slide.]

This give you an idea in study 121 of the benztropine usage at baseline in the four treatment groups, haloperidol in red and the three ziprasidone treatment groups. It is roughly 20 to 30, 35 percent of patients at baseline were receiving benztropine.

During the course of the treatment, the distinction, again, in terms of extrapyramidal symptoms, for the haloperidol group compared to all three doses of ziprasidone.

DR. MALONE: Was benztropine stopped during the study period?

DR. HARRIGAN: Benztropine was continued PRN during the treatment period so that the investigators were allowed to administer benztropine for the treatment of extrapyramidal symptoms. There wasn't a standing daily dose for benztropine.

DR. MALONE: Did the subjects enter the study on antipsychotic already that was stopped or continued or when was the last dosage for antipsychotic before the study?f

DR. HARRIGAN: In study 121, the screening to baseline period was one to two days. And this reflects, really, screening at the time of the beginning of the screening period.

DR. MALONE: I guess what I am trying to figure out is if there were patients on antipsychotics and anti-EPS medicines and then the anti-EPS medicine was stopped, which could have its own rate of EPS apart from the study drugs. For instance, if someone was on haloperidol and benztropine and then you stopped the benztropine before they entered the study, they might have EPS just coming off the benztropine.

DR. HARRIGAN: There is no enforced discontinuation of benztropine. So, by protocol, benztropine was not stopped. Benztropine was permitted to continue and investigators would treat the extrapyramidal symptoms that were being experienced by the patients perceived by the investigators, as needed.

So extrapyramidal symptoms, if they had persisted, would have been treated with benztropine.

DR. MALONE: Was there forced stopping of any other standing medications like other antipsychotic treatment or any other treatments?

DR. SWIFT: Other antipsychotic medications were stopped prior to randomization into the study.

DR. TAMMINGA: What percentage of your patients who entered the study had not had any antipsychotic medication, say, for two weeks or whatever, for a period of time?

DR. SWIFT: I can't specifically give you the

details because we didn't capture it of how long patients had been taking antipsychotic medications prior to entering into the study. However, about 70 percent of those patients entered into 125 and 126 had been receiving antipsychotic medication prior to entering the studies and also a quarter had been taking antidepressants and a quarter had been taking anxiolytics.

DR. MALONE: Do you have a slide that displays how many PRN dosages of benztropine were given per group during the study?

DR. HARRIGAN: During study 121 was the slide that we just--okay. We can summarize during--that was a slide by day. We can look at benztropine use in study 121--do you want to look at the two pivotal studies? This was B92.

[Slide.]

These are the numbers of patients who were administered benztropine at any point during study 125, one of the two pivotal studies. About 15 percent in the 10-milligram group and approximately 9 percent in the 2-milligram group.

B93?

[Slide.]

This is the higher-does ziprasidone IM study. The usage of benztropine is somewhat lower, approximately 5 percent in the 2-milligram group and 8 percent in the 20-

milligram group.

DR. TAMMINGA: Perhaps you could put up that other slide that you had, too, before this of study 121 and explain it in a little bit more detail?

DR. HARRIGAN: Sure. B91. This one?

[Slide.]

What we are looking at here--these are the patients at baseline. So, on entry into the study, at the time they discontinued their antipsychotic medications, these are the percent of patients who are being treated with, who are receiving benztropine, outside of the clinical trial. Benztropine was allowed to continue depending on what the investigator felt was appropriate treatment.

This is the percentage of patients who were being administered benztropine on each day during the three-day intramuscular dosing period.

DR. MALONE: Do you mean new dosages? I mean, additional, apart from what they came into the study on?

DR. HARRIGAN: No. No. For instance, in the 20 and 80-milligram groups, approximately 11 percent of patients on the first intramuscular treatment day received even--or least one dose, of benztropine. For haloperidol, about 23 percent.

Now, on day 2, these figures could be the same or different patients. Anyone receiving benztropine on day 2

would be reflected in this incidence rate plotted here. The intramuscular dosing period ended here, continued into oral dosing, again, counting the same way.

Now, this last datapoint here is the percentage of patients who received at least one dose of benztropine at any time during the intramuscular or the oral dosing period. So, for haloperidol, you are looking at about 55 percent who received benztropine at some time during the seven-day study and, over here, approximately 20 percent, 10 percent, for the 40-milligram group here.

DR. MALONE: I guess what would be interesting would be to know who came in not on benztropine and then who got benztropine added during the study.

DR. HARRIGAN: I can't tell you that. We have not investigated that.

DR. GRUNDMAN: Was that a randomized study? How did the investigators decide who was going to go on the different agents?

DR. HARRIGAN: The treatment groups, the study groups, were randomized so it was a randomized parallel group trial. It was open-label drug administration.

DR. GRUNDMAN: But it was open label.

DR. HARRIGAN: Yes.

DR. TAMMINGA: Dr. Katz?

DR. KATZ: I have a couple of questions. Maybe

you showed this and I missed it. What is the total number of patients who received what you would propose to be the maximum daily dose, which I guess was 80 milligrams. That is what you proposed; right?

DR. HARRIGAN: The maximum daily dose proposed is 40 milligrams. We have studied up to 80 milligrams so we have studied twice the maximum recommended dose.

DR. KATZ: Oh; so you would proposed 20 milligrams given how often? Just twice in the 24 hour period?

DR. HARRIGAN: Not more than twice in 24 hours; right.

DR. KATZ: And the total number of patients who have received that dose?

DR. HARRIGAN: Do you want to go back to the main presentation, the slide with the dosage distribution, probably around 50.

[Slide.]

This is main presentation slide 50. Here we have the distribution. This is the dose, any duration. So 523 patients total, less than 10 milligrams, 18 percent of patients received less than 10 milligrams, a dose of ziprasidone less than 10 milligrams.

If we look at the highest recommended dose, or higher, we are looking at the sum of these two rows, 30 percent, 31 percent, of patients who have received a

daily dose of ziprasidone of at least 40 milligrams a day, up to 80 milligrams.

Here is the percentage. So, 14 percent out of the 17 percent received that much for three days. So, daily for three days. So 27 percent of the patients received at least the highest recommended dose, up to twice the highest recommended dose, for three consecutive days of treatment.

DR. KATZ: How many of those are 20 milligrams within four hours?

DR. HARRIGAN: In study 121, if I could put it back, it was about 70 patients who were randomized to the high-dose group and would have received that dosage regimen.

DR. KATZ: I want to go back again, a little bit, to the PK in multiple IM dosing where the Cmaxes were in the 350 to 400. That is after how many doses, given how frequently?

DR. HARRIGAN: Should we look at the simulation of 20 milligrams given as two doses, four hours apart?.

[Slide.]

What we have done is taken the population pharmacokinetic database. I mentioned over a thousand serum measurements of ziprasidone, collected at various times post-dose, and constructed a model to predict ziprasidone concentrations in 1,000 patients receiving IM ziprasidone at your question, 20 milligrams every four hours for two doses.

We can project that. So, at 20 milligrams, and then four hours later another 20 milligrams--these are 1,000 patients, by simulation--the mean is going to be in the 350 ng/ml range. There will be some individuals with some variability around the mean who have higher and, of course, have lower levels as well.

DR. KATZ: One other question. At the maximum approved dose, which I guess is 80 BID for the oral--

DR. HARRIGAN: Correct.

DR. KATZ: What is the mean Cmax at steady state?

DR. HARRIGAN: In study 054, it is 171 ng/ml. With ketoconozol added, it went up to 220, I think, ng/ml.

DR. MALONE: I guess a safety concern would be that if you had patient coming into the hospital on maximum dose, which could happen, and then they start getting maximum IM dosages for agitation, what would happen to their levels and QTc?

DR. HARRIGAN: You would start the intramuscular dosing on a baseline level of ziprasidone. Now, if they were taking the highest recommended dose and were compliant BID, taking their medication BID, their trough level would be approximately 80 ng/ml. The peak level, as we saw in study 054, about 170 ng/ml.

So, depending on when in the dosing cycle they were administered additional ziprasidone, much as with any

of the other medications that might be administered in that setting, you would superimpose that much ziprasidone--you would superimpose the intramuscular on that much of a baseline. It would be additive at that point.

DR. HAMER: You indicated that you had a relatively small number of people over 65 in the studies and that was why what was done with respect to age differences was cut at 55. Do you know how many people you had over 65?

DR. HARRIGAN: I think the n is less than 10 over age 65. We could look up the exact number.

DR. HAMER: In your proposed labeling, what are you saying about the ages at which this is to be used?

DR. HARRIGAN: We would say that ziprasidone intramuscular has not been studied in the elderly.

DR. OREN: In your pivotal efficacy studies, is it possible to isolate the effect on the BARS scores, for example, starting with the people who had baseline score of 7, and similarly for 6.

DR. SWIFT: There were no patients entered into the studies who had baseline BARS score of 7. We have a handful of patients who entered with baseline BARS score of 6 and I can show you those numbers, just for those entered.

Slide 128, please, from the A file.

[Slide.]

This table displays the number of patients with

baseline BARS score at 6, study 125 on the top, study 126 on the bottom. As you can see, there were ten patients entered into study 125 with baseline BARS score of 6, and five entered into study 126 with baseline BARS score of 6.

Then, underneath, we give you the BARS score at the primary time point in each of the two studies for those particular patients. As you can see, the therapeutic doses of 10 and 20 milligrams did result in larger decreases in the BARS score than the 2-milligram doses.

DR. MALONE: Were the BARS score done right at the point when you were making the decision to give the IM injection for baseline?

DR. SWIFT: The patients had to be deemed eligible by the investigator to be in need of an IM injection and meet those baseline PANSS criterion on the agitation items. The baseline BARS score was done immediately prior to the first injection, and then it was done at fifteen-minute intervals for the first hour and then at ninety minutes, two hours, then hourly until six hours.

Then that sequence of timing of BARS was repeated if they received subsequent injections.

DR. ORTIZ: On your demographics, under ethnicity, I noticed that "other" ranged from about 8 percent to 17 percent. What groups made up "other?"

DR. SWIFT: It was just "other" or Asian. So in

the case-report forms, we captured Asian, black, white or other.

DR. ORTIZ: What about Hispanic?

DR. SWIFT: We didn't separate those out separately.

DR. ORTIZ: So is Hispanic included under white?

DR. SWIFT: I would have to look up that detail, which I certainly will do and get back to you with the information.

DR. HAMER: Do you have any information on the distribution of BARS score, not changes but the scores themselves, at two hours and four hours in the studies for which you evaluated them at two hours and four hours?

DR. SWIFT: Yes; I do, if you will just hold on a moment, I could put up slide No. 256..

[Slide.]

I will take a moment to walk you through this. This is the baseline BARS score versus the scores at four hours primary time point in study 126. Along the vertical axis, you see the baseline BARS scores for the patients entering the 2-milligram group and then, along the top, the number of patients with those BARS score at the four-hour time point, 2-milligram group on the left, 20-milligram group on the right.

The figures in red in the table are those patients

who were unchanged.

DR. HAMER: The way the scaled worked was 1 was essentially asleep and difficult to arouse?

DR. SWIFT: That's correct.

DR. HAMER: So you had nobody who was asleep and difficult to arouse?

DR. SWIFT: No; if you look at the endpoint, you can see that in the 2-milligram group, there was one patient at that primary endpoint who had a BARS score of 1.

DR. HAMER: I am not after the baseline. I want to know what they were at four hours.

DR. SWIFT: Oh; that is four hours. These are the baselines and then these are the one at four hours, four-hour score along the top. So the top line gives you the BARS score at four hours and then the number in parentheses gives you the number of patients who had those scores at four hours.

So, in the 2-milligram groups, there was one patient. In the 20-milligram group, there were six patients.

DR. HAMER: And that is out of roughly 50 in that group, so about 10 percent of your patients in that group wound up so severely sedated they were difficult to arouse.

DR. SWIFT: Difficult or unable to rouse. Perhaps Dr. Harrigan would like to--

DR. HARRIGAN: I think, in trying to get a handle on your question which is how severely sedated is a 1, we looked back at study 121 where patients received a much--a wider dose range and fixed doses of ziprasidone--to examine the effect of ziprasidone fixed doses on the BARS scores and then, to try and get some insight into the BARS score relating to activity and level of sedation.

Let's look at C96.

[Slide.]

In study 121, what we are going to show you is a distribution of BARS score in the four treatment groups. So, we have got the four treatment groups along the bottom. This is 5 milligrams every two hours, 10 milligrams every two hours, 20 milligrams every four hours and haloperidol, haloperidol flexible dose, mean daily dose of 11.

The height of the column reflects the percentage of BARS readings in each of these categories. So, looking first at the haloperidol group, most patients in category 4, quiet and awake, approximate 10 percent of BARS readings in the haloperidol treatment group were a level 5. 0.3 percent were a level 1 of BARS.

Now, if we look at the ziprasidone groups, again, the most common reading is quiet and awake. As you increase in dose, you see a shift from quiet and awake to the left, first into drowsy and asleep, next more into asleep than

drowsy.

Now, the percentage of ratings of a 1, difficult to arouse, are 0.8 percent, 1.5 percent and 0.9 percent. So the readings of 1 are infrequent. Nonetheless. And this is at up to 20 milligrams every four hours.

We wanted to look, though, what does a 1 mean in terms of the investigators. We know that the investigators rates these BARS score fairly tightly but, in trying to get a sense for those these patients were, we went back and looked at the blood-pressure database.

As you recall, at 30 and 60 minutes, in predose, for every patient, we recorded a sitting blood pressure and then another blood pressure after standing for two minutes.

So let's look at 94, C94.

[Slide.]

We went back and looked and said, how many of these blood-pressure readings were missed in each of these BARS groups. So let me start over on the right. First of all, we are looking at the percentage of vital signs which are missing. So, over on the right, there were 11 vital-sign opportunities in patients with a BARS, or where there was a BARS reading of 6, a coincident BARS reading of 6.

Approximately 9 percent of those, so I think that would be 1 out of 11, was missed. Now, the number of opportunities where we had BARS score and blood-pressure

readings coincident, increases obviously because the distribution of the BARS isn't even. Most patients are at a 4 and, at a 4, there are almost 5000 opportunities to look at BARS score and a blood-pressure reading where about 2 to 3 percent of the blood-pressure measurement opportunities were missed.

Over here, in the 1, getting directly to your question, there were 46 opportunities. Again, the 1s were not very common. Of these, 44 of the patients stood up for two minutes and had their blood pressure measured.

There were no serious adverse events of suppressed consciousness. There were no adverse events of coma or inability to arouse. So we would suggest that from this the vast majority of patients were able, when roused, to stand up and have their blood pressure taken.

DR. TAMMINGA: Study 121 was in nonagitated patients?

DR. HARRIGAN: That's correct. The idea here, again, it was the widest dose range, fixed doses so you know what you are getting and what is in each treatment group, and there is no interaction between agitation, I think as somebody mentioned yesterday, release of agitation or lysis of the agitation is accompanied by some increased likelihood to sleep or become drowsy as a relief from the agitation.

So here is what we thought was the best way to

dissect the pharmacologic effect of the drug.

DR. HAMER: Do you have a similar slide for 125 and 126?

DR. HARRIGAN: I think we do. The distribution? Let's look at C99.

[Slide.]

Distribution of BARS score in 125 and 126. No haloperidol group. We are looking at 2 milligrams, 10 milligrams and 20 milligrams. So, again, quiet and awake, the most common reading. Increases in sleepiness and drowsiness, 3.7 percent of all ratings were 1 in the 20-milligram group in agitated patients.

DR. KATZ: It is 3.7 percent of all ratings.

DR. HARRIGAN: Of all ratings.

DR. KATZ: But, from the previous slide, I thought there were six patients which was sort of 10 percent--in one of the studies. I forget which study.

DR. HARRIGAN: You were looking at endpoint before, or at two hours and four hours, whatever--

DR. KATZ: Right. I am just trying to make a distinction between the number of ratings and the number of patients. So there were six. That comes to 10 percent or so. For those patients, did you get beyond the BARS rating? Did you get narratives from the investigator? Do you have a sense of what the patients were like?.

You have some indirect evidence that patients were able to stand up and have their blood pressure taken which implies to you that they really were not terribly unarousable. But do you have a description of what the patients were like?

DR. HARRIGAN: No. A 1 was not considered an event. We didn't obtain a narrative on it. Investigators didn't report it as an adverse event. So the indirect measure of looking at the blood pressure seemed to be objective and standard way to look. We had no other specific narratives of individual cases.

But, as I said, there were no serious adverse events reported in that area.

DR. SWIFT: Of those six patients who ended up with a BARS score of 1 at the primary time point, three did not have any adverse events. Three had events of moderate somnolence and one of those three also had moderate bradycardia, moderate orthostatic hypertension and mild nausea.

DR. RUDORFER: If I can take this out of the BARS and back to the ward for a minute, Dr. Swift, you mentioned before that many of the patients in the pivotal studies went on to oral ziprasidone. So that was at what time point?

DR. SWIFT: The duration of the studies was 24 hours, so there was a double-blind 24-hour treatment period.

Once they had completed that treatment period, they could then enter into the open-label oral extension.

DR. HAMER: Should we be concerned that, in actual clinical practice, clinicians may try to introduce oral antipsychotics as early as possible, maybe even during a day that the patient is receiving IM ziprasidone?

DR. HARRIGAN: If we could look at the main presentation slide with the 20-milligram oral PK and the 10 and 20-milligram IM PK.

[Slide.]

The Tmax of oral and IM administration are quite different, as we pointed out. So here you have a rapid rise and fall with a 10 and 20-milligram intramuscular doses. In the situation you describe where an investigator or a physician, a treating physician, might be inclined to administer the intramuscular and then try to persuade the patient to begin oral treatment, the rapid rise and fall of the ziprasidone concentration following intramuscular administration tapers fairly well with the Tmax of the oral so that it has been at least pointed out to us by some physicians that that is not--this entire slide, actually, represents what might be a fairly common treatment situation.

DR. LAUGHREN: But, again, these are single doses. One question might be if a patient has had several

intramuscular doses, from your earlier data, it appears that those patients may have Cmaxes, from your simulations, up around 600, 700 ng/ml.

Do you know what that curve would look like over time?

DR. HARRIGAN: The falloff is with a half-life of two to four hours so that, even in the extremes of the simulations, there is no accumulation of ziprasidone so that the transition from intramuscular to oral is uncomplicated by long accumulation of residual intramuscular drug.

DR. GRUNDMAN: I was wondering if you have any thoughts about the CGIS or the other secondary efficacy measures that didn't reach significance in the study 125.

DR. SWIFT: We certainly did take a closer look at that as you are aware from seeing the review of the data. The 20-milligram dose was efficacious for all of the primary outcomes and also for a number of the secondary outcomes.

The 10-milligram dose was efficacious based on the AUC and also on a number of AUC-related BARS outcome measures such as the responder analysis but wasn't significant on the CGIS.

There are two points here. One is that the CGIS was intended to be used as a more global measure. It measures many facets of the patient and requires interpretation by the investigator whereas the BARS was

prospectively designed to be a more sensitive measure of the agitated behavior.

So, true, the 10-milligram dose did not demonstrate a therapeutic effect on the CGIS but that is a measure that is less sensitive to the treatment effect. Also, if we look at the number of injections and the timing of the injections in study 125, it provides further support for the efficacy of the 10-milligram dose group.

If I could have slide No. A121, please.

[Slide.]

On this slide, you see the number of patients in study 125 and the number of injections they required, the 2-milligram versus the 10-milligram groups. The blue bars are the 2-milligrams. The green bars are the 10-milligrams. As you can see, more of the 10-milligram patients only required one injection, 37 percent compared to 24 percent of the 2-milligram groups, which resulted in a subsequent lessening of the number of injections required by the 10-milligram group.

Slide A125, please.

[Slide.]

Also, if you look at the time-to-second-injection, there is a significant difference between the two treatment groups in study 125 and the time for patients to receive that second injection.

DR. ORTIZ: Could you review the criteria for the second injection?

DR. SWIFT: Yes; basically it was the clinical opinion of the investigator. So the investigator could choose not to administer any further injections or to administer injections less frequently.

DR. ORTIZ: There was no BARS score or any other scale used?

DR. SWIFT: No; they didn't have to meet the PANSS agitation items criteria that they had to meet at screening and at baseline.

DR. GRUNDMAN: Do you have any thoughts about why, like for example on the PANSS agitation items at four hours, there didn't seem to be any difference?

DR. SWIFT: Well, there is, actually, in the four hours for the 20-milligram group. The studies were not powered to show a difference in the PANSS agitation scores. But they do show numerical trends in favor of the 10-milligram and the 20-milligram groups.

DR. GRUNDMAN: In the 10-milligram group, there was hardly any difference. You would think that it might parallel the BARS but, you know, there seems to be some sort of discrepancy. I am just wondering whether or not the BARS is, like, more sensitive to level of consciousness or something and it is picking up on some sort of a different

quality than some of the other items or secondary scales.

DR. SWIFT: Yes; they are independent but complementary measures. We did have a look at the--and I can show you that in just a moment--of how the baseline BARS correlated with the baseline PANSS agitation scores, but we really felt that they weren't measuring the same things and that the BARS was designed to capture the anticipated acute effect on agitated behavior, the motor behavior of the patient.

I am just looking for the correlation of the baseline BARS in the PANSS.

[Slide.]

This slide shows a comparison of the 125 and 126 baseline BARS score with PANSS agitation items. So we have got the baseline BARS score along the horizontal axis and the baseline PANSS agitation item scores along the vertical axis. This slide is showing you the mean BARS score for each particular PANSS agitation score. So, as you can see, there is a rough correlation and the numbers are giving the n's of those patients.

DR. GRUNDMAN: That actually enhances the point that, at the beginning, it seems like there was a nice correlation between them but, somehow, during the treatment phase, the two scores became a little bit more discrepant.

DR. SWIFT: The PANSS agitation item scores were

not used primarily as an outcome measure. They were a secondary outcome measure in studies 125 and 126. And, as I mentioned, the studies were not powered to show those differences.

The main use of the PANSS agitation was actually in insuring the patients at entry into the study had a quantifiable level of acute psychopathology.

DR. RUDORFER: A diagnostic question. Do you have any more detail on the schizoaffective patients? Were they more manic or more depressed?

DR. SWIFT: I'm sorry; I don't have that information here today.

DR. TAMMINGA: Any additional questions from the committee? I think the committee would like to thank Pfizer for their presentation. Also, we will take a break now, a 30-minute break. So we will reconvene at 10:30. Thank you all very much. Thanks, Pfizer.

[Break.]

DR. TAMMINGA: I would like to restart the second portion of the meeting today to discuss the IM ziprasidone application.

Open Public Hearing

DR. TAMMINGA: I would like to initially call for any public comment. We don't have any public person who has indicated that they want to speak, but I would like to call

for anybody who might want to make a statement during this hearing.

No public comment? Thank you very much. We will proceed with our discussion of ziprasidone IM.

Committee Discussion

DR. TAMMINGA: It has come to my attention during the course of this break that one of the Pfizer advisors who actually had personal experience with conducting this protocol and has some personal experience with, "difficult or unable to arouse," what that might actually mean, could describe it to us. It seemed like that would be valuable for the committee.

So, if you want to go to a microphone, Dr. Zimbroff, we would like to hear your description.

DR. ZIMBROFF: Hello. I am Dr. Dan Zimbroff. I am Director of Psychopharmacology Research at Pacific Clinical Research. At the time of the protocols, I was at Loma Linda University Medical Center conducting these trials.

Let me first say that difficult to arouse--as Dr. Kane and Dr. Tamminga pointed out yesterday, many of these acutely agitated patients have not slept in the preceding twenty-four to forty-eight hours and come in to the emergency department referred for the trials in quite an agitated state.

To get these patients to sleep is often a very therapeutic outcome. When the patients do wake up from sleep, they are often more able to participate in their treatment. They are calmed down, more cooperative and treatment can proceed.

In the BARS table of the 1 to 7, the item is "difficult to arouse." It is not "unable to arouse." It is "difficult or unable." In general, we had no trouble waking up any of the people who became 1. They didn't want to be woken up because this was the first time they had slept in a couple of days. But you could get them up as was evidenced by the very few numbers of blood pressures that were missed.

I also want to say another thing about the BARS maybe if I can flesh it out from the investigative-site perspective. A 5 says overt activity can be calmed, but that is calmed with quite firm verbal limits such as, "Stop it right now." That is the level of intervention that is required to calm down a 5.

By the time someone gets to a 6, you are really unable to calm them down with verbal limits and everybody's fear factor is beginning to rise. It is very difficult to consent a 6, I want to point out. My IRB at Loma Linda, like many university IRBs, takes it job very seriously and was very concerned about the ability of these agitated

psychotic patients to give a good and true informed consent.

As a check on that process, the IRB appointed consent observers. The consent observer and I consented every patient and we were just not able to get more than one patient who was like a 6 on the BARS who we felt could give a good informed consent. There were many 6s that we just did not feel could give a consent.

So I think that is why the preponderance of the patients in the trials are at the 5 level and there are relatively few 6s. A 7 patient who is violent and in restraints is, obviously, someone who could not give informed consent to a trial.

One other point that I wanted to make from listening to this morning; those CGISs that, in my opinion, should have been done at two hours at the point when you would expect maximum effect from that first injection, they were done at four hours when the 10-milligram shot is definitely tapering off in its effect. The 20-milligram dose is holding on at four hours but the 10-milligram one is fading away.

I had large numbers of patients on both 10 milligrams and 20 milligrams and, clearly, the 20-milligram dose was more efficacious, although there was some efficacy with the 10-milligram one.

DR. TAMMINGA: Does anybody have any questions for

Dr. Zimbroff? Dr. Hamer?

DR. HAMER: So a 4 was essentially normal; right?

DR. ZIMBROFF: No; I wouldn't say that a 4 is normal. A 4 can be extremely psychotic. In fact, a PANSS of 90, someone can be very hallucinating, very delusional, have loose associations, have many negative symptoms.

DR. HAMER: Let me phrase that another way. A 4 was essentially nonagitated?

DR. ZIMBROFF: Was not particularly agitated or could be calmed with reasonable verbal limits.

DR. HAMER: So, since you basically didn't have any 6s or 7s and 4 is not agitated, you sort of had a two-point scale, not-agitated and agitated, not really a seven-point scale.

DR. ZIMBROFF: There are degrees of agitation. In essence, I think that we all did the best we could within the constraints of the U.S. civil-libertarian ways that we are not going to treat anybody involuntarily who doesn't give informed consent. We are not going to do chemical restraint in a study. We are going to get as agitated patients as we can who can give an informed consent.

That is, in essence, what we--we did the best we could in the circumstances which we were in to try to test this medication for the purposes for which it was created.

DR. SWIFT: I just wanted to add another point,

that 70 percent of the patients in the study met the entry criteria that you heard yesterday for another IM antipsychotic agent. So there is consistency in the baseline results.

DR. HAMER: You mean in the investigator's judgement.

DR. SWIFT: Yes.

DR. HAMER: And the investigators are motivated to bring in subjects if it is competitive enrollment.

DR. ZIMBROFF: I would have to say that I am not going to give a shot to someone who doesn't need a shot regardless of whatever competitive enrollment is going on. You are not going to make up a patient and put him in a category that he is not in to get patients into a study. We are trying to test a medication in agitated patients.

Another factor that goes on is that you consent someone and then you have to draw their blood and wait for their blood to get back from the lab. In essence, while you are waiting for these stat labs to come back, you are almost doing a 1 to 1 with this patient because it is a pretty agitated patient. You can't start treatment in the study until you have these stat labs back meaning that he qualifies.

There certainly is some therapeutic effect going on when you are doing this 1 to 1 for a few hours with this

patient, doing your best to calm him down and to keep things from getting out of hand. It is a pretty chaotic situation in the emergency department or on the unit where this person has been directly admitted in an agitated state.

So I don't know this for sure because there is no data but there was some drop off from the time when people signed up to when they actually got their first dose. There was some drop off in their agitation level because we were "1 to 1-ing" them.

DR. HAMER: When they got their first dose, was their level of agitation rerated at that point?

DR. ZIMBROFF: It is rated just before the first dose.

DR. HAMER: So that is a different rating than the pre-lab screening rating.

DR. ZIMBROFF: Yes. There really is no screening BARS. There is a baseline BARS which is just before the first injection.

DR. SWIFT: Actually, I just wanted to make one more comment, if I may, about the competitive enrollment and investigators being encouraged to enter patients into these studies. Most of the sites doing studies 125 and 126 were also conducting study 121 which has virtually inclusion/exclusion apart from the criteria of requiring IM treatment and having acute psychopathology at baseline.

So if you had a clinically stable patient, there was an alternative study which the investigators could enter the patient into. Also, the BARS is really an instantaneous assessment. It is a snapshot of a patient at a moment in time. So it is possible that investigators have rated a patient as being in need of IM therapy. They have met the baseline PANSS agitation items scores criteria indicating they have acute psychopathology.

But they might have just been sitting there quietly when the investigator comes in to rate them at that particular moment in time.

DR. MALONE: I just wanted to say I thought that including the clinician requirements that they thought that the patient needed IM medication is probably the best thing you can do because I don't think, no matter what rating scale you use, you could rate somebody as high and still not thing they need medication, or be kind of at the border but yet still think they need medication. So I think that is probably the best check you could have.

Regarding consent, I am just a little confused. For instance, someone could come in to the hospital and be calm and you know that they have periods of agitation. You can consent them when they weren't agitated and then, later on, they become agitated and get their first dosage.

But it seems like that is not how you did it.

DR. ZIMBROFF: No. I don't think that my IRB would--that, in essence, would be like a preconsent, in the event that you become agitated, would you sign up now to give advance for this future time. I don't think that my IRB would have tolerated that.

We had to get them at the time, which is the horns of the dilemma.

DR. MALONE: Yes; that would be a dilemma. I guess some IRBs vary in what they might allow to do.

DR. TAMMINGA: I would like to just check a minute probably with Dr. Swift. I guess it would be in response to the comment that Dr. Hamer made about the two-point scale. My concept of this, and I just want to check it out to see if this is it, is that the diagnosis of agitation in need of IM treatment would be more like a diagnosis and that what we have here in the BARS is a rating scale, not a diagnostic scale, and it would be a rating scale that spans the breadth of behaviors from difficult to arouse to highly violent so that, over the course of behaviors, this is a seven-point scale but it is not a scale for agitation.

Would you make a comment on that, Dr. Swift?

DR. SWIFT: I am not sure I could actually phrase better than you have just worded it, apart from actually maybe putting the slide up again with the items on. But your understanding is correct. It is a continuum of the

levels of activity of the patient, the BARS.

DR. HAMER: Not to be an overly picky statistician or anything--

DR. TAMMINGA: We count on you for that.

DR. HAMER: But if, indeed, whether a scale is intended to be a seven-point scale spanning the entire breadth of ratings, if it turns out that, in a particular sample, 90 percent of the ratings are either 4s of 5s, then effectively it is a two-point scale.

If you are going to do a statistical analysis of it, you would then want to choose a technique that is appropriate for a two-point scale rather than a seven-point scale. That was one of the reasons why I wanted to look at the distribution of baseline scores.

Now, in this case, one of the benefits of using a area under the curve was that it introduces more fine gradations and distributions into what they used as their outcome variable so that, in fact, maybe that wasn't as much of a concern.

Also, just on a slightly different subject, one of the things that I liked about this set of trials was the fact that they didn't use their outcome measure as part of their entry criteria. In my opinion, that ought to be more commonly done. It is all too possible in trials, if someone scores just below a minimum score on an entry criterion to

kind of, without any malice of forethought, sort of kind of bump the guy up a point to be able to get him into the trial and then, magically, on the next rating, the score drops a little bit and you have what appears to be something like a placebo effect.

In this case, by using different instruments for the entry criteria than the one they use for their baseline and outcomes, that goes a long way towards ameliorating that particular piece of the problem.

So I think that was a good thing to do here and I would encourage sponsors to do that sort of thing in the future.

DR. TAMMINGA: Thank you. I would like to see if anybody else on the committee has additional questions for the Pfizer team.

DR. GRUNDMAN: I was wondering if you have the mean BARS scores after first injection for study 125 extended out to four hours so we could see the entire spectrum of efficacy out to four hours on the BARS because there was a suggestion made that maybe the efficacy was wearing off at four hours and that might explain the discrepancy with the other secondary measures.

DR. SWIFT: If you could put up A23, please.

[Slide.]

We did, indeed, look at the BARS scores out to

four hours after the first injection and this slide has both of the pivotal studies on it, time-after-first-injection on the horizontal axis and mean BARS scores on the vertical axis.

DR. GRUNDMAN: With the 20-milligram dose, it seems like the efficacy was maximal at two hours. With the 10-milligram dose, it doesn't seem like there was really any difference between the two and the four.

DR. SWIFT: This is based on the mean BARS scores.

DR. GRUNDMAN: Right.

DR. SWIFT: As you recall, we used the area under the curve so that we captured the treatment effect across the time interval.

DR. HAMER: And were there any second injections in here somewhere?

DR. SWIFT: Yes; this is all patients. In the 10-milligram group, nine of the 2-milligram patients and eight of the 10-milligram patients received a second injection sometime between hours 2 and hours 4.

If you are interested, I can show you a breakdown with just the patients who received one injection.

DR. HAMER: Please.

DR. SWIFT: Slide 162, please.

[Slide.]

This gives you the AUC for study 125, all

patients. I have got this one up so I will let them take a look at this and see if they want to see any more.

DR. HAMER: Thanks.

DR. TAMMINGA: Any additional questions right now of the committee for any of the Pfizer presentations?

Thank you very much, Dr. Swift.

I think we will begin our deliberations of the questions that have been addressed to us; has the sponsor provided evidence for more than one adequate and well-controlled clinical investigation that supports the conclusion that IM ziprasidone is effective for the treatment of agitation. The indication would be agitation in schizophrenia and schizoaffective disorders.

Would anybody like to begin this discussion? Dr. Katz?

DR. KATZ: I would just like to maybe amend the question, or at least have the committee think about it in a slightly different way, and that is with regard to dose. You have two studies. One is at 20, one is at 10. Just, theoretically, let's say, for purposes of discussion, if we found that a 20-milligram dose, there were safety questions that remained to elucidated, it would be useful for us to know whether or not the committee thought there was substantial evidence of effectiveness at the 10-milligram dose.

Ordinarily, again, substantial evidence, we would require at least two trials. If we were to approve a drug, let's say, at 20 milligrams, a trial a 10 milligrams would support--if you had two studies that were positive, one at 10 and one at 20, it would support the approval of the 20-milligram regimen.

But if you have two studies, one of which is at 20 and one of which is at 10, and you rule out the 20 for some safety reason, then you are left with one study at the lower dose which would not necessarily constitute substantial evidence at that lower dose.

I know this sounds a little complicated but, basically, if we could hear about what you think about efficacy at the two doses that were studied, that would be, I think, useful for us.

DR. TAMMINGA: I had an opinion, actually, about the dose characteristics of this study in that I was delighted to see a study where doses differentiated from each other. There always is the prescription, if you will, that we don't really need placebo-controlled studies in psychiatry or in the study of psychotic illnesses because all you need to do is show that one dose is different from another.

That has really been almost impossible in the studies that have been done so far, but this study shows a

really nice dose-response relationship between 2, 10 and 20. Even though the 10 and 20 were not done in the same study, for me, that the response to 2 milligrams in each study was so similar makes it more convincing to look at as a dose group.

Also, what I would say in response to your question, Dr. Katz, is that, at least when we asked the sponsor about the efficacy of the 2-milligram dose, if you compare the two-hour and four-hour times--I forget what it was that they said when they compared, either the two-hour or the four-hour time, to the baseline of the 2-milligram group, there was a significant decrease in agitation, so that would at least be some indication that the 2-milligram dose might have some efficacy in its own.

Dr. Hamer?

DR. HAMER: I hate to disagree with our chairperson, but, basically, I have seen so many uncontrolled studies in which before differs from after on placebo that the fact that before differed from after for 2 milligrams, I don't find real convincing.

DR. OREN: Perhaps this was surely was dealt with yesterday afternoon and if what I am saying is at odds with the discussion which I missed, I certainly withdraw my concern, but I want to go back to the 6 and 7 as the enrolling point with regard to the fundamental efficacy

question because I think, certainly, in milder agitation, a beautiful job has been done in demonstrating the efficacy of medication.

The concern that I have is that the population, perhaps, that will need it the most are the 6s and 7s who we are not having the chance to observe. I realize, certainly, the impossibility of getting informed consent in 7s and the difficulty in obtaining pre-consent, although I do know that, for example, at the NIH with the intramural program when they do studies of Alzheimer's patients, wherever possible, they do obtain pre-consent precisely to address such issues.

But what makes this different, for example, from an antidepressant trial where, again, in a typical antidepressant study, I realize the average patient is not on the verge of suicide when they enter the study, the fact is that most antidepressant patients who would be receiving a oral formulation would not be at that level.

The difference here is that we are talking about an IM formulation which is presumably intended for the most acutely agitated subjects. So a concern, and I haven't answered, myself, and maybe the group answered it yesterday, is was this sample sufficiently agitated for efficacy to have been shown in the population that would probably get it in the real world?

DR. TAMMINGA: And then we tried to address the additional question, would there be reason to believe that efficacy would be different in the severely agitated than in the moderately agitated to a greater degree or to a lesser degree.

Does anybody have comments on Dr. Oren's--

DR. GRUNDMAN: I think we saw some data earlier this morning looking at the more severe versus the milder cases and I don't think there was any differentiation. Is that my recollection?

DR. OREN: The problem was there were only 10 essentially in a group of six, so it is hard to derive much information from that.

DR. TAMMINGA: We did see data yesterday afternoon comparing the more agitated and the less agitated and the effect was actually stronger in the more agitated. But, in that dataset, similarly the number of highly agitated people was quite limited.

Would you like to propose a solution to your problem?

DR. OREN: One possible solution would be to, perhaps, through such mechanisms as pre-consenting or a study focusing on 6 to try and gather data specifically, more data at that end of the spectrum and, perhaps, a smaller sample size might be sufficient to demonstrate it.

In some ways, I would bet that this drug is effective in the higher groups. We just don't have a lot of data to support that.

DR. KATZ: Just to fill Dr. Oren in, the absence of many very agitated, severely agitated, patients in yesterday's dataset was no bar to the committee voting to say they recommend approval. So labeling can deal with, to some extent, the description of who was in the trials. There are a number of ways to do that.

DR. TAMMINGA: And it was pointed out that this is not a particularly unusual situation. For instance, in depression studies, depressed people who are suicidal are generally excluded and things like that.

DR. OREN: That is certainly true. The biggest difference is that this particular formulation is something that--as opposed to the typical depression study where the average person taking antidepressants is not necessarily on the verge of suicide or on the verge of restraints. This particular formulation is directed at the far end of the spectrum.

DR. TAMMINGA: Dr. Kane has something to say?

DR. KANE: (John Kane, Pfizer) I think a similar point was made in the discussion yesterday just in terms of the level of agitation and so forth. If you look at the patients who got the lowest dose, about 75 percent of them

went on to get subsequent injections. So that supports the notion that the clinicians were making a judgment even after entry into the study that this patient needed yet another injection.

DR. TAMMINGA: Addition discussion on this issue? I would like to draw the committee's consideration back to the dose issue that Dr. Katz raised and generate some discussion on the efficacy of the 10-milligram dose.

DR. MALONE: I don't know if I want to ask first. There was a slide that showed how many second and third doses of medication they got by dosage which might be interesting to look at 10 versus 20.

DR. TAMMINGA: Would you put that up, Dr. Swift?

DR. SWIFT: I think it was A121 that had the 125. I am just looking for another presentation that has the studies on it. A119, please.

[Slide.]

Here you can see the number of injections required in the 24 hours, both studies 125 on the left, 126 on the right. The green, blue, lilac and red areas in each bar represent the number and percent of patients requiring one, two, three and four injections in both the treatment group.

DR. MALONE: They look fairly similar to me, the 10 and 20. The 2 doesn't look that different either, but the 10 and 20 look very similar. I would think that would

be a good outcome measure is how many times you had to get more injections.

DR. GRUNDMAN: Do you have a graph--for the 10-milligram study, it would be nice to see a second measure which could confirm the BARS. Maybe the CGI improvement? At least that one seemed to have some trend in the right direction. I was wondering if you could maybe show another graph of another measure which paralleled the primary outcome measure.

DR. SWIFT: I had shown previously the time-to-second-injection which is significant for 125 which is a non-BARS-related measure of efficacy which is slide A125.

[Slide.]

DR. GRUNDMAN: That is similar to what we saw before. I was just wondering, on the clinical global impression, that is a totally different scale. I know it wasn't significant, but it would be nice to see--

DR. SWIFT: Actually, that was in the main prescription, if you could put the CGIS up from 125.

[Slide.]

Not the CGIS. The CGII.

DR. SWIFT: I'm sorry; I beg your pardon. If we could put up slide A107, please.

[Slide.]

Okay. And 174; this is the PANSS agitation items,

similar to--using the same criterion that you heard yesterday.

[Slide.]

DR. TAMMINGA: Is that the same slide for 126?

DR. SWIFT: I think it should be with slide 175, 174, please.

[Slide.]

DR. TAMMINGA: Maybe you could put up the one that you just had up.

DR. HARRIGAN: In A174, we are looking at patients with three of those four agitation items with scores of at least 4. You are looking at the change from baseline in the PANSS agitation score so that you see directional improvements for the 10-milligram dose group both in the hour-4 time point and at the last time point.

Here we even split out on the right side--this is in the more agitated patients--those who received one injection only versus the 2-milligram group.

DR. SWIFT: A98, please.

[Slide.]

DR. TAMMINGA: These lack significant dots because there are not significant differences, but they show the numerical difference between the groups; is that it?

DR. SWIFT: That's correct.

DR. TAMMINGA: Dr. Hamer, would you like to make a

comment.

DR. HAMER: No.

DR. TAMMINGA: Does this answer your question?

DR. GRUNDMAN: Yes. I think it sort of shows that the trends are at least following the primary outcome measure.

DR. TAMMINGA: And there seems to be not that much difference between the 10 and the 20-milligram qualitatively.

DR. HARRIGAN: Let me try and clarify. We did flash some slides, but A175 will match the A98 that you just saw. So A175, we went, after reading the briefing document for the compound you looked at yesterday--we went back to our database and looked at the excited component which was the endpoint we looked at yesterday.

So in patients who had at least a score of 4 on three of those items, this is a subset of the patients. So this is the more agitated patients at hour 4 and at last. Then, on the right side, as we pointed out, at that hour-4 time point, some people had two injections, some people had one injection.

So, on the right side, we were looking at patients who had one injection only of 2 milligrams or 10 milligrams. So this is the excited component, the same five items that you looked at yesterday. Again, there is a directional

change in favor of 10 milligrams. In A98, just to bring you back home, you have got the same directional change in the excited component, the same endpoint that you looked at yesterday with n's, as you see here, 20 to 40 per group.

DR. TAMMINGA: Comments on the dose question?

DR. OREN: I think, since clinicians always have the opportunity to go beyond the prescribed dose if they are not seeing the desired effect and given that the 10 and the 20 milligrams seem to be in the same direction as far as efficacy, I would not think that an additional efficacy study would be required if, for safety reasons, the 20-milligram formulation couldn't be initially approved.

DR. TAMMINGA: Does anybody else want to make a comment on that?.

DR. GRUNDMAN: I would tend to agree. I think there is some efficacy at the 10 milligrams. It is not as robust as it is at the 20 milligrams, but I think there is evidence from the primary measure and some supportive evidence from the secondary measures that there is some efficacy.

DR. TAMMINGA: And we are not looking at placebo-controlled data. We are looking at dose-response data.

DR. KATZ: I recognize that you feel, and I would agree, there is some evidence it is an internal sort of confirmation of one of the three primary outcome measures

that was positive, when the data was looked at in various different ways, time-to-second-injection, whatever you want to consider, or the PANSS excited component.

Ordinarily, in approving a particular dosing regimen, again, if it is in this direction of dose, we would ask for independent replication, another study which confirms that, in fact, what you saw in the first study was true.

So that is really sort of the question, I guess. I suppose you could believe there is enough internal confirmation to say that you don't need a second study at that dose, but that would be quite unusual.

DR. GRUNDMAN: Then I think you can go back to the argument that was just made before that if you need to go from 10 to 20, there is still that option.

DR. KATZ: Yes; but at the moment, theoretical case, that you think the higher dose is not sufficiently established to be safe, it is an option you might--

DR. GRUNDMAN: That is 40, though; right? That is 20 twice.

DR. KATZ: Right.

DR. GRUNDMAN: Here we are talking about 10 twice.

DR. KATZ: Oh; you mean to go to a second dose of 10.

DR. GRUNDMAN: Right. I think that is what you

were saying before.

DR. KATZ: I still think you are left with the question of independent replication.

DR. TAMMINGA: Although you are left with a question of independent replication, in both of the studies, the 2-milligram dose had nearly the same effect. So it does give one some confidence in the similarity of the two studies, in addition to all the design similarities between them.

DR. MALONE: I don't recall any discussion of this, but why was 2 milligrams used instead of placebo?

DR. TAMMINGA: Dr. Swift?

DR. SWIFT: When we were designing the studies, we polled over 40 sites that we intended to use during the double-blind pivotal studies. The overwhelming majority voted in favor of a 2-milligram-dose design as opposed to a placebo-controlled design.

DR. GRUNDMAN: Was that for ethical reasons, or comfort? What was the rationale there?

DR. SWIFT: Two reasons. One is the investigators' opinion that they felt it would be inappropriate in this clinical setting to administer placebo. And, also, many of them, most of them, determined that it wouldn't get through their IRBs, it would be unacceptable.

DR. ZIMBROFF: Just to supplement Dr. Swift's comment there, I had two discussions with my IRB chairman about this at Loma Linda and he told me there was no possible way that the IRB was going to approve a placebo-controlled study in acutely agitated patients, that they felt it was unethical to withhold any kind of treatment from them.

They also sent me some literature from an IRB journal which shows that over 60 percent of the United States IRBs at that time were not approving placebo-controlled studies for acutely relapsing schizophrenic patients. So there was just no way that it was going to happen at our university if there was a placebo control.

DR. MALONE: I think we looked at PRN usage in children one time, and I think the most effective PRN, regardless of what you put in it, was a needle. So it does make some questions about actually just getting a needle injection, for IRB's information, could have quite some effect on many patients. In fact, nurses use it all the time.

They give you the option of an injection versus an oral dose at times. I think just the offer of an IM injection does have quite an effect on patients.

DR. GRUNDMAN: Also, didn't we see some placebo studies yesterday and some comparator studies yesterday that

were double-blind and randomized? I think those would sort of be a more optimal design if they were available.

DR. TAMMINGA: The placebo-controlled studies would tend to lower the maximal agitation level of people enrolled in the study, one would guess.

DR. GRUNDMAN: Presumably, the treatment differences would be greater and the drug would appear to be more efficacious than it is now.

DR. HARRIGAN: We wouldn't take the position that it would be inappropriate to do a placebo-controlled trial or that it would be impossible to do a placebo-controlled trial. We wanted to conduct our pivotal studies entirely within the U.S. and I think the two studies in schizophrenia where you saw yesterday 500 of those 600 patients enrolled outside of the U.S.

We wanted to conduct those studies in the U.S. and we judged that there was some resistance from IRB's to conducting that kind of a trial. On the basis of that, and with some confidence that the drug would have a dose response, we thought that the most prudent thing to do would be to conduct a dose-response trial which we thought would give us valid efficacy results.

DR. HAMER: I don't have any problem with that, all other things be equal which, of course, aren't equal all of the time. Beating 2 milligrams has got to be harder than

beating placebo unless the 2 milligrams has no effect at all. So they beat a higher hurdle, to mix metaphors. If, in their opinion, it would have been difficult to get IRB approval with a placebo arm and they chose to go ahead and use 2 milligrams, I have no problem with that.

DR. TAMMINGA: This is the kind of design that really a lot of the patients and voluntaries are really clambering for, this kind of a non-placebo-controlled design. In many ways, the company deserves some commendation for really doing a strong dose-response design to demonstrate that you can really show differences between doses.

I don't want to get away from making sure that Dr. Katz has all the information he wants to about the 10-milligram dose. I hear people saying that the 10-milligram dose is clearly an effective dose compared to 2 milligrams and that the 20-milligram study might offer some support in that direction.

Dr. Oron?

DR. OREN: I guess I would amend my previous comment to say that if there was concern about the 20-milligram dose from a safety point of view and you were going to be relying just on the 10-milligram-dose study, that does put more of an impetus on wondering what is needed to demonstrate efficacy in the 6s and the 7s because, in

particular, they might need the higher dose.

If one was going to ask for more data from company, I would think that focussing specifically on that group would be the critical question.

DR. TAMMINGA: I would like to focus the committee's attention a little bit on the diagnostic groups or on the focus group. The company is suggesting that they have demonstrated efficacy against agitation and schizophrenia and schizoaffective illness. On the other hand, when they did their studies, they really took all comers and the fact that they have increased numbers of schizophrenics and schizoaffectives would really be accidents of the demographics of the illness.

It might be that, with the caveat of not having been studied in the elderly, which is certainly hasn't, that they might really have demonstrated efficacy against agitation in a group of psychotic disorders.

I would like people to comment about that.

DR. HAMER: These studies used pretty small sample sizes. The two pivotal studies used a total of a couple of hundred subjects. By definition, that makes doing virtually any kind of subgroup analysis impossible, so that, although they were able to demonstrate that 10 or 20 milligrams beats 2 milligrams, if you ask virtually any question, males versus females, races, age, et cetera, and certainly

diagnosis here, you just flat out don't have the data to do that.

Given that there were probably only a few people with many of these diagnoses, I would feel uncomfortable, I think, drawing the conclusion that this drug is effective in those diagnoses.

DR. TAMMINGA: Doesn't what you just said, though, argue against specifying diagnoses? If the intent of the study was to look at the effect of this drug in agitation in psychotic disorders, and if you can't legitimately look at subgroups, you just say that it is efficacious or not efficacious in the nonelderly psychotic disorders.

DR. HAMER: If you intend to make a sort of a claim for all comers, then I would say you probably need to design your studies with sufficient sample size so that you have a sizeable subset in a wider variety of all comers than you have here. It would be similar to a study in which I demonstrated that drug A beat drug B and, for whatever reason, 90 percent of my sample was female and I had relatively small samples sizes.

I would be slightly uncomfortable drawing the conclusion, perhaps, that it works in males.

DR. LAUGHREN: It seems to me that this is the issue that we spent a lot of time talking about yesterday and the committee, it seemed to me, came down on the side of

thinking that you can't lump all these different agitations together. You can't make the assumption that the pathophysiology, perhaps, is the same even though clinically agitation make look the same in patients with schizophrenia and schizoaffective disorder and bipolar, that we wouldn't want to make that assumption that it is all the same.

So I would be troubled by a recommendation that, here, for this application, you could extrapolate to all psychotic disorders. As is pointed out, you have very few patients with any of these disorders other than schizophrenia and schizoaffective.

DR. RUDORFER: There is another related issue that--I don't want to get beyond the purview of the committee, but, clearly, we have established that in using IM antipsychotics, we are talking about, for psychotic patients, the initiation of treatment that will extend beyond, often beyond, 24 hours into oral, more long-lasting therapy.

I think one lurking question, which we really don't have data to address, is whether we should think in terms of the IM medication as matching what is planned for the oral; that is, we have seen now, in these two pivotal studies, most of the patients who were given IM ziprasidone then took the option of continuing on oral ziprasidone.

I don't know if we want to, or if it is

appropriate for us to, consider the issue of whether IM ziprasidone is most appropriate or only appropriate for psychotic patients who are planned to continue on oral ziprasidone. Again, that comes back to the diagnostic question, since, if oral ziprasidone is approved for schizophrenia, then I would think it would make sense to limit the focus of the approval of IM to that same subgroup.

DR. TAMMINGA: Any additional comments on the efficacy question or any additional questions that the committee should consider?

DR. KATZ: It hasn't really been explicitly discussed, but I assume the committee believes that the study at 20 milligrams was a clearly positive study.

DR. TAMMINGA: What I would like to do is just go around the table and get a statement of your position on efficacy on the first question. It is not that we necessarily need to vote right now. Has the sponsor provided evidence for more than one adequate and well-controlled clinical investigation that supports the conclusion that ziprasidone is effective for the treatment of agitation in schizophrenia and schizoaffective diagnoses?

Why don't you start, Dr. Oren?

DR. OREN: With the limitations that I expressed before, I would say yes, they have established that.

DR. TAMMINGA: And you may articulate those again.

DR. OREN: With regard to the severity of subjects.

DR. GRUNDMAN: I think that there is efficacy on the primary outcome in the 10-milligram trial and I think there is some supportive evidence for efficacy on the other measures. And I think there is evidence at the higher doses, at 20 milligrams, that it is effective. So I would say that trendwise it is effective and, leaving it up to the clinician to provide another dose if the first initial dose of 10 milligrams wouldn't meet the therapeutic outcome that was desired, I think that it would be all right.

DR. HAMER: I think they have demonstrated efficacy and the fact that they demonstrated efficacy beating 2 milligrams as opposed to beating placebo, and the fact that we make them predesignate a primary response variable. In the 10-milligram study, they beat 2 milligrams on their primary response variable. I think that is support for efficacy.

DR. GRADY-WELIKY: I would agree with what has been said, particularly with Dr. Oren's point about the severity issue, although I was somewhat relieved by what the investigator mentioned in terms of characteristics of the folks who were entered into the study.

DR. MALONE: I agree that they demonstrated efficacy. I think it is harder without a placebo because I

think a lot of people who are agitated have a peak level of agitation which decreases no matter what you do. But I think, given that, that they did demonstrate efficacy.

DR. ORTIZ: I agree that efficacy has been demonstrated.

DR. RUDORFER: Yes; I agree efficacy has been demonstrated.

DR. TAMMINGA: My position would be that efficacy has been demonstrated. So if we could just get a show of hands of efficacy, yes, around the table.

[Show of hands.]

DR. TITUS: We have eight yeses and no no's.

DR. TAMMINGA: Now we will go on to the question of safety. The question here is has the sponsor provided evidence that ziprasidone is safe when used in the treatment of agitation at the doses that they have specified.

DR. MALONE: I think they have demonstrated--I guess the big issue for ziprasidone is QTc and they have demonstrated that, in the subjects they treated with the IM, it was as safe as the oral. The only question that remains in my mind is what would happen of somebody came in with a full load of ziprasidone and then, on top of that, got full loads of IM ziprasidone.

DR. TAMMINGA: Dr. Katz?

DR. KATZ: I can't answer that question directly,

but I would like to sort of focus the committee's attention on the question of QTc. We have a fairly good idea from the oral about what the effects on the QTc are at a particular plasma level. The sponsor did a formal study--it has been discussed--which looked at--I guess it looked at the effect on the QTc at Tmax of an 80 BID dose which gives you--we heard the Cmax, at that dose, is somewhere around 175 or something like that.

The mean Cmax after the second dose of 20 milligrams IM is twice that, 350 to 400, we heard. There is very little human experience, at least well-monitored EKG experience so far as I know at plasma levels in that range.

One of the things the committee recommended when we discussed the oral product was that, in postmarketing, there should be a further evaluation dose response above the doses--about 80 BID. So, the way I see it, we have very little well-monitored experience about what the QTc is doing at the plasma levels that, in general, will be reached in some patients because they will reach higher plasma levels after at least the second dose.

If, in fact, the first dose of 20 milligrams IM, the mean Cmax is somewhere about 225, if I remember the numbers correctly. We don't have very much well-monitored EKG at that level either, although I believe, in study 54, the Cmax probably approached that when the drug was given

with an inhibitor. I don't remember exactly what the Cmax was there, but I think there was 30 percent increase, or something, so 30 percent of 175 gets you at about 225, if I have done the math.

So, there, maybe we have some comfort from a well-designed study that looked at this but, at the higher plasma levels that people will get at the sponsor's proposed regimen after the second dose of 20, it appears as if we are into levels where we really don't have very much good information about the effect on the QTc and the committee was certainly interested in that with regard to the oral after its approval.

So I would like to hear what the committee says about that.

DR. TAMMINGA: Dr. Hamer?

DR. HAMER: My concern really reflects what Dr. Malone said as well as, in some sense, the kind of reverse of what Dr. Rudorfer said. Dr. Rudorfer was concerned about what would happen if you started someone off on IM and then switched them to oral.

Dr. Malone is concerned about the reverse and I am concerned about that, too. If you have an existing patient who has been medicated for quite a while on the maximum labeled dose for oral ziprasidone, that person could be floating around with an existing relatively steady-state

plasma level in the, what, 170 to 200 range.

You get relatively quick doses of 10 or even 20 milligrams on top of that, the plasma level could well--if I interpreted this stuff correctly--could well be up there in the 500 range, the peak concentrations.

We have virtually no information on what happens at those kinds of levels. They had a strong efficacy effect size and they were able, thus, to demonstrate efficacy with relatively small sample sizes. One of the consequences of that if they have those relatively small sample sizes to try and look at safety in rare events and it is very problematic.

DR. TAMMINGA: Have we heard everything from the company that you have to say about the relationship between dosing and plasma levels and plasma levels and QTc changes?

DR. HARRIGAN: I think it might be useful to invite Dr. Tom Ludden who has studied the pharmacokinetic database with the intramuscular formulation to, perhaps, summarize and answer any questions the committee might have.

DR. LUDDEN: Let's start back at slide 56 from the Ludden file.

[Slide.]

It is kind of a situation of the glass is half empty or the glass is half full. There is a tendency to focus on the highest values here, the extremes. In

actuality, you kind of lose track of the fact that the mean values from this--we are really looking at a very small percentage of individuals that are going to achieve these highest levels.

DR. KATZ: I thought we were told that the mean Cmax from this data, from these simulations, was somewhere in the 350 to 400 range.

DR. LUDDEN: We have a mean profile.

[Slide.]

That is the mean profile from that same data. The first dose peaks out at around 200, the second dose a little over 250 from the mean of those. That is, again, the stochastic look of this. We are looking at the high end. On a high end, you go up forever. On the low end, you have a got a truncation at zero. Things don't get as small as they get large, so the mean tends to set a little lower than it looks.

DR. KATZ: Do you know if we have seen this data? Has this data, or these analyses, been submitted? Again, we were just told, if you look at the simulation of a thousand, we were told it was 350 to 400. Now we are seeing it is 250.

DR. HARRIGAN: It is an incorrect statement.

DR. KATZ: Okay. But, again, have we seen the data? Has it been submitted to the agency for our review?

DR. LUDDEN: I don't know whether the simulations have been submitted?

DR. HARRIGAN: No; the simulations haven't been submitted. You have got the components, in terms of you have got the plasma-level reports but not the--

DR. LUDDEN: The population analysis was submitted, as I understand it, on which this was based. Could I show a couple of other regimens just before--maybe slide--

DR. TAMMINGA: Let's see if we have any additional questions, if you would wait a minute on this. Dr. Hamer?

DR. HAMER: So you don't happen to have a simulation of predicted Cmaxes in patients who are already carrying on board a full long-term dose of ziprasidone.

DR. LUDDEN: No, we don't. But it would be fairly easy to simply add, I think, the peak levels, if you want to do a worst-case scenario, to the levels one is seeing here on the mean to get an average estimate of that. It is on the order of 400, I would imagine, or 450.

DR. HAMER: Which would mean that a proportion of the patients would have Cmaxes higher than 400.

DR. LUDDEN: There is certainly that possibility; yes.

DR. KATZ: Obviously, these are simulations. You haven't formally studied Cmax in patients who have received

this regimen?

DR. LUDDEN: Let me look at slide 13. This may help a little bit.

[Slide.]

13 from this is actual data. It is a small study. It is the 046 study. This is the 20-milligram dose every four hours, except for the very first dose. In that study, they got 10 milligrams for that very first dose.

The second day has kind of got a strange profile to it because a lot of data wasn't added to simulate out the profiles completely. But the first day and the third day had fairly intensive sampling. So these are six real subjects that have experienced the drug and really at 20 milligrams Q four hours times four, which is larger than what has been done.

But that is, I believe, the best quality data we have to address this.

DR. TAMMINGA: What is the n in this study?

DR. LUDDEN: I think this particular subgroup was six. There were other groups at other doses, but I think there were six here.

DR. TAMMINGA: This is 20 milligrams four times a day?

DR. LUDDEN: Yes; times three days. The other thing to pick up on this is that there is no accumulation

from day to day with this kind of regimen.

DR. TAMMINGA: Just because you don't have any yellow dots on the second day doesn't mean they weren't getting the dose.

DR. LUDDEN: Right.

DR. TAMMINGA: It just means you weren't taking the plasma levels.

DR. LUDDEN: There were no observations there. The profiles are predicting that; yes.

DR. HAMER: You said Q4 hours.

DR. LUDDEN: Yes.

DR. HAMER: So, since there are twenty-four hours in a day, that means there was eight hours between their last dose one day and the first dose the next?

DR. LUDDEN: There was actually probably twelve hours because there are three four-hour intervals. There are four doses.

DR. GRUNDMAN: How was this administered? IM or oral?

DR. LUDDEN: This was IM. Actually, the worst-case scenario here, the top peaks, look very close to the means that we have seen from the predictions from the population analysis.

DR. TAMMINGA: So if these people had begun this regimen on a therapeutic dose of ziprasidone, you could add

a certain plasma level but only to the first few because you wouldn't necessarily tend to give them concurrently.

DR. LUDDEN: For the first day, you would add that. So you would be pushing 350 to 400. But not 700. That is the good news.

DR. TAMMINGA: Additional questions on these particular slides? Have we seen all the information you have on QTc changes at the highest doses? That was a single slide that you showed us.

Discussion? Comments?

DR. GRUNDMAN: This may have happened last time when you discussed the oral version, but overdoses? Is there any data from overdose that might pertain here in terms of levels?

DR. TAMMINGA: Even though we did talk about it last time, since it has come up, I think it is important to cover whatever there is to cover.

DR. HARRIGAN: We have limited data. There were three individuals who received initial doses of 30 milligrams intramuscular for ziprasidone. I can show you three individual narratives for each, but there were no remarkable adverse events. There were no ECGs done at around those times and no levels done in those individuals that I recall. If they were, they were factored into the pharmacokinetic modeling.

DR. GRUNDMAN: How about with the oral dosing, the oral agent?

DR. HARRIGAN: With the oral agent, we have seen doses up to 3 grams, 3,240 milligrams, taken in an overdose situation. We had included in the presentation in July several overdose cases. There were no ECG effects. There were no cardiovascular adverse events.

In one of those cases, ECGs were obtained sequentially at from two to seven hours after the overdose. That was the 3-gram overdose. There was no--I think the largest change in those ECGs was 15 to 20 milliseconds.

DR. KATZ: Could you say something about the variability of the plasma levels, IM versus oral?

DR. HARRIGAN: I would invite Dr. Brater, Dr. Craig Brater, from Indiana University to help Dr. Ludden.

DR. LUDDEN: I will respond. Could I have slide 90, please. Is that the one, Tom?

[Slide.]

This was a study comparing, in phase I, PO and IM. It summarizes the mean AUC of 10 milligrams single-dose. You can see that, IM, it has about a 21 percent coefficient of variation for AUC, 25 for Cmax. A typical oral dose, 40 milligrams BID. It has about 50 percent or 60 percent more variability. So, actually, the IM as measured by Cmax and AUC in this study is less by about 40 percent.

DR. KATZ: You wouldn't expect that to change with increasing dose of either one of those.

DR. LUDDEN: It tends to be dose proportional in AUC. Actually, the Cmax, as you go up in dose, tends to be a little less. That hasn't been completely factored in to the simulation. So our simulations may be a worst-case scenario even more so than we have depicted. That would need to be worked up in more detail.

DR. KATZ: I know you discussed this a little bit earlier, but I am interested in the well-monitored QTc at the highest dose regimen, let's say at Tmax after a second dose of 20 milligrams IM. You presented a table I believe which attempted to get at that, but I would just like a little bit more detail about that.

DR. HARRIGAN: I think you are thinking of the slide in the main presentation that was mean change by time after dose.

DR. KATZ: Right.

DR. HARRIGAN: May I have No. 69--70; let's look at the next one.

[Slide.]

This is the graphic form.

[Slide.]

Then, in 70, we tabulated in two-hour increments. Now, what I was pointing out at the time, I think, is that

if you look across the 20-milligram row, there are 14 plus 5 is 19 and 8 are 27 individuals who have an ECG done within those time windows after a 20-milligram dose.

Of those 27, 15 had that ECG done after the fourth 20-milligram dose. Then we can break it down. For seven of those, it was after the first 20-milligram injection, for five after the second injection, zero after the third injection and 15 was after the fourth injection.

DR. KATZ: Okay, but Tmax, you would expect, would be where after the second dose or after the third dose or the fourth dose?

DR. HARRIGAN: Cmax should be between zero and two hours or approximately one hour after the--

DR. KATZ: So the first group of columns is where we want to look. How many of those 14 was that measurement taken after the second, third or fourth dose?

DR. HARRIGAN: I am going to look for help from my colleagues because we have broken in down for the 27. I am not sure if we have broken it down for the--maybe we could find that out.

DR. KATZ: You see where I am going.

DR. HARRIGAN: Sure.

DR. KATZ: Again, study 054 was designed to look specifically at this sort of question. I am trying to see if you have that kind of data already for the second dose.

DR. HARRIGAN: We should be able to--can we get it? Russ, I don't have the answer right now. Hopefully, we will be able to dig it out. We know from study 046, at least six of them it was after the fourth dose because six of those 14 patients had an ECG timed to one hour after the fourth dose of the second day.

So at least six of the 14 were, in fact, after the fourth dose. How many of the other eight were after the fourth dose, I can't tell you. But in study 046, in those treatment groups, we timed the ECG to approximate the Cmax.

DR. TAMMINGA: Do you want to keep looking or do you want us to go on to another topic?

DR. HARRIGAN: You better let us keep looking.

DR. KATZ: While you are looking, in study 054, how many patients were in each drug group?

DR. HARRIGAN: Between 25 and 30, close to 30; 28, 29, 31. If we could put that last slide up with the table, slide 70.

[Slide.]

It was trying to match that conceptually exactly what you are doing with study 054, which caused me to put this on the slide. With this number of patients, we calculated a confidence interval of -5 up to 18. Then, if you look at study 054, in the ziprasidone group, 31 patients, the mean estimate was somewhat higher. The

confidence interval, again, in the worst end of it, at least, clearly overlaps what was seen with the IM and underwrites our expressed opinion on the range of QTc change seen and predicted with IM.

DR. KATZ: But, again, the numbers may be very much smaller than 14 in that cell.

DR. TAMMINGA: Other QTc-related questions or discussion that we would like to hear?

DR. KATZ: We are waiting for what, exactly? Are we waiting for the number, the actual number? We know there are at least six and we are not going to get that today; is that correct?

DR. HARRIGAN: We don't know if we will have it today or not. We are optimistic--if the database will yield it. All fourteen, at least, it would be to an initial dose of 20 milligrams. The six, representing four doses of 20 milligrams would be in excess of the proposed recommended dose range of up to two 20-milligram doses.

DR. KATZ: Right. I understand that. But you think that, at least in the near future, that is the best we are going to do? That's fine. I just wanted to know whether we should keep waiting or move along.

DR. SWIFT: We don't have it readily available.

DR. HARRIGAN: I suggest you move along.

DR. TAMMINGA: We have been assured by the company

that we have seen all the data that they have prepared to show today, although they have additional formulations of the data that they would be willing to present in the future.

DR. KATZ: Presumably, at some point, you will get to the question of whether or not--the second question about whether or not safety has been established.

DR. TAMMINGA: We are discussing safety now.

DR. KATZ: Right, but, again, I am sort of anticipating a vote. I still think there is some information that we need to look at more closely internally for these simulations and that sort of thing and the answer to these questions which I think are important.

I suppose we can proceed with the presumption, or with the assumption, that everything is as the sponsor says it is. If we find, upon review, something that is different than we have heard here, we would have to take whatever your recommendation is accordingly. But I would suggest maybe that is the best way to proceed.

DR. TAMMINGA: I would agree with that recommendation and I think that the committee ought to function as though, upon the FDA's review of the rest of the data, that the QTc changes will be consistent with what we have just seen.

DR. GRUNDMAN: Do we need the empirical data

regarding the questions that have been raised before about whether or not, if somebody is on stable or a high-dose of ziprasidone, whether or not additional IM injections--do we need empirical data or just the simulations and additives would be sufficient.

DR. TAMMINGA: We have as much empirical data and as much simulation data as there is for us to consider. The company suggested that, in order to consider what would happen with a combination of oral and IM data, we would add together the baselines.

I guess what provides a bit of comfort is that this is a relatively short half-life compound as we saw from the actual plasma levels after the Q-four-hour IM injections.

DR. KATZ: I don't believe we saw any information, any data, on that whether it was empirical or a simulation. You will have to decide whether or not you think--if you think everything else is okay, whether the absence of that data is important or whether it should affect labeling or whatever you think.

I think, as far as the short half-life, it is fairly true. I don't know, really, how much is known about how long you have to be at a Cmax in order for you to get into the time of risk. But, anyway.

DR. HARRIGAN: I can fill in. Three of the

fourteen were after the first dose of 20 milligrams. Three were after the second dose and eight were after a fourth dose. So there was 14 altogether. Three were after the first dose. Three were after the second dose. And eight were after the fourth dose.

DR. KATZ: So it is a total of eleven patients--

DR. HARRIGAN: Beyond the first dose.

DR. KATZ: Beyond the first dose.

DR. HARRIGAN: Right.

DR. MALONE: When you give us the half-life for the IM preparation, what is the range of half-lifes? I guess we are usually seeing the average half-life. Is there some kind of range you can give for what you might expect in patients for half-life beyond just what the average is?

DR. BRATER: (Craig Brater, Pfizer) It is 2 to 4.

DR. MALONE: So no one had a longer half-life than 4 in any of your studies for IM preparation?

DR. BRATER: I don't have the individual data. I am not sure--is that the absolute range? Individual data ranged from 2 to 4 in the single-dose studies which is where that was looked at. So 4 was the outer limit.

DR. TAMMINGA: Thanks.

We have spent a considerable time discussing QT safety data. There is also the motor side-effect data which, in the comparative study they did between haloperidol

and the fixed doses of ziprasidone, it deserves mention that the motor side-effect data was considerably better for ziprasidone than for haloperidol although there was evidence of some akathisia at the higher doses.

Anybody who would like to comment on that or discuss it further.

DR. MALONE: To some degree, I thought it was hard to say what ziprasidone--I thought it was low, the EPS. But it might even really be lower because it seemed that you could come into the study already on another antipsychotic. So it was nice to low EPS data. I think it could even be lower.

DR. GRUNDMAN: I just have a question more out of curiosity. One of the side effects that seemed to be dose related was insomnia. I was just wondering, given that the drug tends to have these sedative properties, why that might be.

DR. TAMMINGA: Would you like to comment on that, Dr. Harrigan?

DR. HARRIGAN: There is some incidence of insomnia with the atypical antipsychotics but with the oral formulation of ziprasidone as well. The studies were truncated at two hours or at four hours. They were, at minimum, 24-hour studies and study 121 was a three-day trial. So there is some incidence of insomnia that has been

described already.

DR. TAMMINGA: Is there any more discussion on the safety issues? If not, I think we probably ought to go around the room and give our opinion on safety. I would like the committee--yes; Dr. Oren?

DR. OREN: Just one question before we go around the room. This is to the FDA, to Drs. Laughren and Katz. Is the data on the QTC prolongation that has been presented here substantially different from the database that was available at the time of your initial review?

DR. KATZ: Different in the sense of the degree of prolongation, the results, or whether it is just a different database?

DR. OREN: Different database and the results, both. In other words, are we seeing substantially the same data that was available at the time of the division's initial review?

DR. KATZ: I don't know. You probably heard what we thought of the actual prolongation in study 054 for the oral. So I don't know how different it is. The one thing about the data, slide 70, I think it was, that chart, there is no real control group. I guess you have haloperidol as a control group. The prolongation at 0 to 2 hours is longer than you see in haloperidol, the mean.

It is 6.4 milliseconds to haloperidol is

5 milliseconds. There is considerable overlap in the range. Those are confidence intervals, I know what those are. But it is a question as to how to interpret that data. We have to look and see what we thought haloperidol was as a control.

That is IM haloperidol. Oral, we believe it doesn't have much of an effect. How much of an effect it has when given in these doses, whatever the doses were, IM, is a question. I don't know the answer to that. There were other drugs given. In study 054, obviously, there was a whole range of drugs given.

We sort of thought of haloperidol as the ersatz placebo there. But that was oral haloperidol. This is parenteral haloperidol where there is a suggestion. I believe that there is some QT prolonging effect. So it is hard to know how to interpret this.

DR. HARRIGAN: I think that, actually, yesterday were some of the only haloperidol IM QTc's we have seen. I think in the database yesterday, they were looking at the QTc change on the same order or less than what we are describing here on slide 70 for haloperidol. That was with a Bazett correction which, I think, might have altered it a little bit in that direction. But I think that is the only perspective that I know.

DR. TAMMINGA: For the present consideration of

today, the committee needs to assume that the FDA and Pfizer have already made their decisions based on advisory-committee input on the relationship between oral ziprasidone, plasma levels that result from oral dosing and QTc. That is really a matter of public record.

What we have to consider today is the IM plasma levels that result from the new dosing pattern that we are seeing, now the new dosing route and pattern, and the relationship of those plasma levels to QTc and whether or not those plasma levels fall within the larger safety database.

DR. KATZ: Just to further complicate things, it is not necessarily just the plasma levels which, again, if the simulations and the relatively sparse data, actual empirical data, on plasma levels that we have seen after an appropriate regimen, if they turn out to be--we think that they are as we have heard, that would be one thing.

But there is quite a different, as the sponsor has pointed out, rate of rise or time it takes to get to that maximum plasma level with IM as opposed to oral. That might have something to do with risk. I have no idea if it does, but it is a different pattern. I don't know how much information we have about that.

That is why I am looking for some empirical, well-monitored study 054-like data, relatively robust data,

looking at QT with this particular presentation of the Cmax. I don't know if it is only Cmax that puts you at risk. It could be the rate of rise to it.

DR. TAMMINGA: I think it is probably time for a statement of the committee's--Dr. Grundman?

DR. GRUNDMAN: Maybe we can just get an idea of whether or not we think the drug is safe except for this QT issue because, if that is the case, then maybe we can just remand that QT issue to Dr. Katz and Dr. Laughren to figure out.

DR. TAMMINGA: Of course, that is the core of it, though.

DR. KATZ: I suppose one option is--we are raising some questions that we are concerned about. The question is whether or not you feel that these questions have been appropriately answered by the sponsor and whether or not you feel they are critical questions.

If you think they are critical and you think the sponsor hasn't adequately addressed them, you could vote one way. If you think they are critical and you think the sponsor has adequately addressed them, you could vote another way. Of if you don't think they are critical, yet another way, although I think you only have two options.

So I don't think I can help you much more than that.

DR. GRUNDMAN: The question, I guess, was to vote with an exception, with this particular issue remaining to be figured out.

DR. TAMMINGA: Dr. Katz has suggested that we vote with the assumption that the sponsor will present to the FDA data sufficient to convince them that is consistent with the data that we saw, so I would suggest to the committee that that is the kind of thing that we vote on.

Surely, if there are hidden dragons there, the data that they subsequently present to the FDA will demonstrate that.

Any additional comments?

DR. KATZ: Again, as I say, one other option is to say you need more data. We posed these problems, and we have asked these questions. I would be interested, for example, to hear if there is anything known about the effect of the rate of absorption on risk.

You are shaking your head. Yes; well, there may not be any information about it and we have to think about whether or not it is the kind of thing that is at least potentially sufficiently problematic that you want more data on that. Or you might think there is enough.

We know there are eleven patients who have gotten the second dose and had their QTc measured. Again, it is not really a controlled study. It is hard to know what that

means, but you could say, "We need for more information."

DR. TAMMINGA: One of the problems about the QTc question that we are discussing now and the relationship between QTc and rare adverse cardiac events is that they are so rare. So we would have the choice, I guess, between accepting the data that we have now or otherwise recommending a gigantic IM study that would provide enough data to really answer the questions that you are asking which seems a bit unlikely.

DR. KATZ: Right. Even with the oral, we didn't really expect, necessarily, to see any clinical events which is one of the reasons why we did this very well-designed, well-monitored, fairly small study. In study 054, you heard there were 31 patients who got ziprasidone in that study.

So I wouldn't suggest that we do a 10,000-patient study. The question is whether or not we have enough data now a la study 054 which was, basically, a requirement on the sponsor before approval, to say that we are not concerned, we are not any more concerned about this than we were with the oral.

DR. TAMMINGA: I am not sure that the committee would be content saying that they are not concerned, but that the level of concern somehow is balanced by the level of benefit that this compound would bring.

Additional comments?

DR. RUSKIN: My name is Jeremy Ruskin. I am from Mass General in Boston and I am a consultant to Pfizer. The issue of rate of rise is a very important and interesting one and, unfortunately, one for which there is no data. It would be very hard to know exactly how to collect it because of the issue of hysteresis. So you would have to, in essence, give an IM bolus and record EKGs literally every minute for a significant period around Tmax to get some sense of what was happening.

Even with that, it would be hard to know when to stop because the maximum effect on IKR may, in fact, not occur at the time of peak concentration. So I think it is a very legitimate issue to raise. It is a very difficult one to study and get an answer to.

The other issue that is of some interest, and we are getting very theoretical here, is that IM drugs are not always associated with more potent QTc effects than oral. For example, quinidine is more potent in its effect on IKR given orally than it is parenterally.

That is probably due to the fact that there is an oxide metabolite which has most of the effect and you don't see the first-pass metabolism with it. Therefore, you get hypotension but you don't get as much QTc effect with IM quinidine.

With ziprasidone, there is less M9 generated with

IM. M9 is a more potent IKR blocker than the parent compound. So, theoretically, and, again, this is purely hypothetical, one might actually see less QTc effect per milligram of IM than with PO. But these are questions clearly for which we don't have data.

DR. KATZ: As far as your first point about you wouldn't necessarily know how to do it because of hysteresis, is there any reason to believe that phenomenon would be at work with IM and not with PO? We made an assumption, in study 054, and we generally make this assumption and we may be completely incorrect, that we measure the EKG at Tmax and that's what we have.

You could certainly measure the EKG at Tmax. It has been done in a few patients here. Even though the Cmax may be the same oral and IM at these different regimens, it might matter how you got there, how quickly you got there and you would only know what the effects were once you got there. But it would be something.

DR. RUSKIN: I don't disagree at all. I think it is a very important question and one for which we don't have data with any drug that I know of. The changes with IM, obviously, are much more rapid so you have got much less of a window in terms of knowing where to place your EKGs and where to sample.

With oral, I think it is a much slower rate of

rise, obviously, and a slower decline. If you have got four or five EKGs, the odds are you would hit the maximum effect. I just wouldn't know how to design that with the IM. But could it be done? Sure. You would just need a lot of EKGs.

DR. KATZ: Ostensibly, it has been done in some patients already, at least the attempt has been made. There are a few patients who you believe you captured Tmax after the second or third IM dose.

DR. TAMMINGA: Dr. Hamer?

DR. HAMER: It is probably even harder to measure at Tmax because there is individual variation. So you could measure what your population pharmacokinetics tell you is Tmax on a population model. But, for the individual patients, trying to then look at relationship between rate of rise when you really are not quite sure what the rate of rise is in any particular patient and trying to time your EKGs. You would have to be taking sort of blood samples and EKGs every five minutes.

DR. TAMMINGA: I think that it is time for the committee to give their opinion on the safety of this compound in the IM form based on the data that the company has presented and based on the consistency of any future data that they will be able to present to the FDA, itself.

Dr. Oren, would you like to start?

DR. OREN: Sure. I really feel I can only give a

comment in regard to the present data and this is only recommendations so that, if future data changes things, it is obviously the FDA's decision to do what it wishes.

I am still haunted by the participation of the cardiologists in the oral meeting, at the oral ziprasidone meeting. So with some of that concern still being present, I am not comfortable that safety has been established.

DR. GRUNDMAN: I think that, from the standpoint other than the QT data, I think there is good safety for this drug. It seems to me that is the main concern. I think it would be reasonable to maybe do another study just to look at this issue. I think that would be a good idea. We have heard from the company and from the FDA representatives that that might be the only way we are going to get answers.

So I would say that safety has been demonstrated except for the one item.

DR. HAMER: I actually think that--not that I want to put words into either Dr. Katz' or Dr. Laughren's mouths, but this is one instance where I think that careful labeling can probably handle a lot of this and maybe motivate the sponsor into doing further study.

I do think that this drug has been demonstrated as safe as long as it is not given following enough oral ziprasidone to get the blood level up prior to the IM

ziprasidone, and also as long as it is not in either pediatric or elderly populations.

If it is basically ziprasidone-naive patients getting the recommended IM doses, I am relatively comfortable.

DR. GRADY-WELIKY: I would agree, mostly with Dr. Hamer's opinion, particularly around the question of--since oral ziprasidone just got approved, we don't have any experience of what is happening out there or what is going to happen when they get an IM injection. That is a bit concerning and so I would say to look carefully at the labeling. I would encourage you, in FDA, and the sponsor to consider some type of formal study around what happens to those folks who are treated with oral ziprasidone and then given IM injection because we don't know. We don't have the data.

And so I think that would be important data to have. It could be that nothing happens. So that would, I think, be really important. But I think the benefit of the other safety measures of this drug in terms of the minimal motor effects is important to keep in mind, too.

DR. MALONE: I think because of the concern about the QTc and the lack of data about what happens with you add IM to PO that we don't have enough information to say that it is safe. I think it is likely that patients will be

treated with PO ziprasidone and then enter hospitals.

I think the likely thing for a clinician to do is then take the IM formulation of the drug that the patient is on. So I think that is going to happen if they are both out there so that we should have some data about that before saying it is safe.

DR. KATZ: Can I just ask you to clarify? So you would not be in favor of approving it even with labeling that says, make sure the patient is ziprasidone-naive, or is x number of hours away from the last dose of oral ziprasidone.

DR. MALONE: No; I am not. I am not recommending that you--I wouldn't be saying you would need a big study, but I think you should get some data about what would happen giving IM to PO before you would say it was safe.

DR. ORTIZ: I think, in answer to Dr. Katz' question, I would be comfortable with a warning for patients who are on oral ziprasidone given the data we have seen.

DR. RUDORFER: I would like to amplify that. At the risk of opening a closed issue, I would just point out that, even in terms of efficacy, we did not see any data in the pivotal studies on patients who became agitated during oral ziprasidone treatment. So, by definition, everyone who had been on an antipsychotic was taking something other than oral ziprasidone when they entered the pivotal IM study.

DR. TAMMINGA: But the drug has only been recently approved so that there wouldn't have been that opportunity, really.

DR. RUDORFER: Right. But we don't know clinically how much sense that would make anyway if somebody gets agitated in the face of oral ziprasidone whether it even makes clinical sense to use IM ziprasidone. My point is I want to second and third the idea that it sounds to me, on the basis of the data we have, that IM ziprasidone, from the safety point of view, most reasonable essentially for initiation of what will be oral ziprasidone treatment.

I would agree that, from the safety point of view, and maybe from efficacy but definitely from the safety point of view, its use in ziprasidone-naive patients would be safest. I think the safety otherwise has been established at the 10-milligram dose but I would like to see more data on the higher dose before I would consider it safe.

DR. TAMMINGA: Again, just a point of clarification. You would like to see more data before you consider the 20-milligram dose safe in patients who had been on ziprasidone or on anybody?

DR. RUDORFER: No; in anybody. Particularly, I am concerned about the use of repeated doses of the 20.

DR. KATZ: Is it the QTc issue that is of concern?

DR. RUDORFER: Yes. We have raised issues in

terms of both the high plasma levels and the rapid rate of rise to those high plasma levels that simply the data become very, very sparse.

DR. TAMMINGA: My opinion is given in the context that the agency will actually satisfy themselves that all of the data that the sponsor has is consistent with the data that we have seen. In addition to that, my opinion is formulated under the umbrella that all of us would always want to see more data than there is about all these questions since there is insufficient data at every turn of the way about it. I don't disagree with that.

But my own opinion is that the company has presented data that would suggest that this formulation of ziprasidone is safe as presented. I gained increased confidence when we saw the repeated dose, 20-milligram plasma-level data after IM administration, that the drug didn't accumulate and plasma levels didn't continue to grow.

It would be my opinion that the management of the entering on ziprasidone oral issue be managed in labeling. I wouldn't necessarily think that ziprasidone-naive would be necessary but maybe a certain period of time since any previous dose of ziprasidone might be the way I would advise to handle it. So that is my personal opinion.

We have to decide on something to vote on. The mc has some varying opinions. I wonder if somebody has an

overwhelming proposal that might tie these opinions all together. Dr. Katz?

DR. KATZ: You can certainly do that. I don't think, even though we have posed it as a formal question to vote on, I think we have a sense of where each member of committee stands on whether or not you think we need more data before it should be approved or whether or not we can deal with it in labeling.

I don't know that a vote is absolutely necessary.

DR. TAMMINGA: Does either of you or both of you want to say an additional word?

DR. LAUGHREN: No; I would just back up what Rusty said. I think we have a fairly clear idea of where everyone stands on both efficacy and safety in the current state of the data.

DR. TITUS: I have a vote. I don't know about you, but I have a vote.

DR. TAMMINGA: Then we are not going to go around the table and vote on any single proposition. So we will just end the meeting with the opinions that have been expressed and the opinions that we have with the FDA.

Thank you all very much. Thanks to the sponsor for the presentation.

[Whereupon, at 12:23 p.m., the meeting was adjourned.]